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Treatment of Drug-Dependent Individuals With Comorbid Mental Disorders

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Treatment of Drug-Dependent Individuals With Comorbid Mental Disorders

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Introduction

Lisa Simon Onken, Jack D. Blaine, Sander Genser, and Arthur MacNeill Horton, Jr.

Drug use disorders are frequently associated with mental disorders. Data from the Epidemiologic Catchment Area (ECA) study (Regier et al. 1990) showed that over half (53 percent) of individuals who have a lifetime diagnosis of a drug use disorder also have a lifetime diagnosis of a mental disorder. Approximately two-thirds of individuals with a cocaine or opiate use disorder have, at some point in their lives, had a mental disorder. For those with a lifetime diagnosis, 15 percent have had a drug use disorder. Twenty-eight percent of schizophrenics and 42 percent of those diagnosed with antisocial personality disorder have had a drug use disorder.

Despite the common co-occurrence of drug use disorders and mental disorders, persons who have both of these problems tend to fall between the cracks of service delivery systems. Individuals with mental disorders who seek treatment in the community may receive it within the mental health services system, and drug-addicted individuals may receive treatment within the drug abuse treatment system. Those requiring treatment for both mental and drug use disorders may not be able to receive comprehensive treatment in one treatment program. In the worst case scenario, the clinicians responsible for the treatment of the mental disorder may not have any idea about what is going on with the addictive disorder (e.g., treatment or severity) and the clinicians responsible for the addiction treatment may not be aware of what is happening with the mental disorder. Unfortunately, those persons who have concurrent mental and addictive disorders are not easily accommodated by the current treatment delivery system.

Having separate service delivery systems and separate Federal institutes funding research on mental and addictive disorders has generally fostered the separation of mental health and addictive disorder research. Typically, research on the treatment of mental disorders is addressed within the research programs of the National Institute of Mental Health, while research on the treatment of drug addiction is addressed within the research programs of the National Institute on Drug Abuse. Research on both drug use and mental disorders may, at times, be viewed with skepticism by reviewers who value the "homogeneous" samples needed to decrease "error variance." It is entirely plausible, however, that there are circumstances in which different individuals with the same set of

and drug use disorders are more alike than different individuals who have only one disorder. Assume, for example, that there are many types of depression and many possible etiologies of depression. From this assumption, it is clear that a study of people with depression is a study of a very heterogeneous group of people. Assume, also, that nicotine affects only people with a certain type of depression in a certain way, and that these are the people who become addicted to nicotine. In this scenario, those individuals who have a homogeneous type of depression coupled with nicotine addiction may be more like each other than a group of heterogeneously depressed people who are not addicted to nicotine. This scenario seems quite possible in light of Glassman's work (this volume) on the relationship between depression and nicotine.

Research on the treatment of individuals with comorbid mental and addictive disorders holds promise for a greater understanding of the relationship among these disorders and the potential for better treatments. To date, however, research in this area has been limited. A meeting was held on September 27 and 28, 1994, to highlight some of the ongoing research in this area and to stimulate further research. Not only was research on the treatment of comorbid mental and addictive disorders addressed, but the additional problem of human immunodeficiency virus (HIV) in the context of these comorbid disorders was a topic of focus. The findings presented at the meeting could not be viewed as a definitive statement on this complex subject. On the contrary, only a limited number of combinations of comorbid mental and addictive disorders have been researched, and no one type could be fully addressed within the confines of any one meeting.

The meeting was chaired by Lisa Simon Onken, Ph.D., Jack Blaine, M.D., Sander Genser, M.D., M.P.H., and Arthur MacNeill Horton, Jr., Ed.D. of the National Institute on Drug Abuse. Presentations were given by David Barlow, Ph.D., Robert Brooner, Ph.D., Kate Carey, Ph.D., Linda Cottler, Ph.D., Francine Cournos, M.D., John Docherty, M.D., Alexander Glassman, M.D., Bridget Grant, Ph.D., Edward V. Nunes, M.D., Kim Mueser, Ph.D., Bruce J. Rounsaville, M.D., Paul Satz, Ph.D., Andrew Shaner, M.D., and George Woody, M.D. The presentations given by these scientists underscore the promise that research on comorbid mental and addictive disorders holds for future treatment advances and resultant public health benefits.

Just as the meeting could not fully address the full range of comorbid mental and addictive disorders and associated HIV issues, neither can this

monograph. However, the chapters that follow, written by many of the participants of the meeting, are examples of exciting research being done in this important area, and they help to define the need for further research. It is the hope of all the editors of this monograph that the readers will be inspired by the contributions that follow.

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The Influence of Comorbid Major Depression and Substance Use Disorders on Alcohol and Drug Treatment: Results of a National Survey

Bridget F. Grant

INTRODUCTION

The co-occurrence of alcohol use disorders, drug use disorders, and major depression has frequently been reported in alcoholic, drug abuse, and psychiatric patient samples (Allen and Francis 1986; Demilio 1989; El-Guebaly 1990; Ross et al. 1988; Rounsaville et al. 1982). Significant associations between substance use disorders and major depression have also been found in general population surveys (Regier et al. 1990; Robins et al. 1988; Weissman and Meyers 1980), but the magnitude is much lower than that reported in clinical samples. This suggests that people with comorbid substance use disorders and major depression may be more likely to seek alcohol or drug treatment than those without such comorbidities. However, to date, no studies have examined the impact of comorbidity on alcohol or drug treatment in the population of greatest clinical and policy relevance, that is, among those persons with an alcohol use disorder or drug use disorder not found in the treated population.

The purpose of this study was to separately compare the comorbidity status of persons with alcohol and drug use disorders who did or did not seek alcohol or drug treatment, respectively. Separate comparisons were also examined for major types of treatment facilities, including 12-step group programs and inpatient and outpatient facilities.

METHODS

Sample

The study was based on the 1992 National Longitudinal Alcohol Epidemiologic Survey (NLAES), a nationwide household survey

sponsored by the National Institute on Alcohol Abuse and Alcoholism (Grant et al. 1992). Field work for the study was conducted by the Bureau of the Census. During the survey, direct face-to-face interviews were conducted with 42,862 respondents, 18 years of age and older, in the contiguous United States and the District of Columbia. The household response rate for the NLAES was 91.9 percent, and the person response rate was 97.4 percent.

The NLAES featured a complex multistage design (Massey et al. 1989). Primary sampling units (PSUs) were stratified according to sociodemographic criteria and were selected with probabilities proportional to size. Approximately 2,000 PSUs comprised the 1992 NLAES sample, 52 of which were self-representing—that is, selected with certainty. Within PSUs, geographically defined secondary sampling units, referred to as segments, were selected systematically for each sample. Oversampling of the black population was accomplished at this stage of sampling in order to have adequate numbers for analytic purposes.

Segments were then divided into clusters of approximately four to eight housing units, and all occupied housing units were included in the NLAES. Within each household, one randomly selected respondent, 18 years of age or older, was selected to participate in the survey. Oversampling of young adults, 18 to 29 years of age, was accomplished at this stage of the sample selection to include a greater representation of this heavier substance-abusing population subgroup. This subgroup of young adults was sampled at a ratio of 2.25 percent to 1.00.

Diagnostic Assessment

The survey questionnaire, the Alcohol Use Disorders and Associated Disabilities Interview Schedule (AUDADIS) (Grant and Hasin 1992), included an extensive list of symptom questions that operationalized the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV) (American Psychiatric Association 1994) criteria for alcohol/drug use disorders and major depression. These questions are described in detail elsewhere (Grant et al. 1994). Past year DSM-IV drug-specific diagnoses of abuse and dependence were first derived separately for alcohol, sedatives, tranquilizers, opioids (other than heroin), amphetamines, cocaine (and crack cocaine), cannabis (and THC and hashish), heroin, methadone, and hallucinogens. A composite measure of any of these drug use disorders (except alcohol) was then constructed.

Consistent with the DSM-IV, an AUDADIS diagnosis of alcohol or drug abuse required that a person exhibit a maladaptive pattern of substance use leading to clinically significant impairment or distress, as demonstrated by at least one of the following in any 1 year: (1) continuing to use despite a social or interpersonal problem caused or exacerbated by the effects of use, (2) recurrent use in situations in which substance use is physically hazardous, (3) recurrent use resulting in a failure to fulfill major role obligations, or (4) recurrent substance-related legal problems. An AUDADIS diagnosis of substance dependence required that a person meet at least three of seven criteria defined for dependence in any 1 year, including: (1) tolerance; (2) avoidance of withdrawal; (3) persistent desire or unsuccessful attempts to cut down or stop using; (4) spending much time obtaining a drug, using it, or recovering from its effects; (5) giving up or reducing occupational, social, or recreational activities in favor of use; (6) impaired control over use; and (7) continuing to use despite a physical or psychological problem caused or exacerbated by use.

Diagnoses of alcohol and drug abuse and dependence also satisfied the clustering or duration criteria of the DSM-IV. The duration criteria of the DSM-IV include the requirement for a clustering of symptoms within any 1-year period, in addition to associating duration qualifiers with certain abuse and dependence symptoms. The duration qualifiers are defined as the repetitiveness with which symptoms must occur in order to be counted as positive towards a diagnosis. They are represented by the terms "recurrent," "often," and "persistent" appearing in the description of the diagnostic criteria.

Consistent with the DSM-IV, the AUDADIS diagnosis of major depression required the presence of at least five depressive symptoms (inclusive of depressed mood or loss of pleasure and interest) nearly every day for most of the day during any 2-week period. Social and/or occupational dysfunction must also have been present during the disturbance, and episodes of major depression exclusively due to bereavement or physical illness were ruled out. The reliabilities of the diagnoses of DSM-IV alcohol and drug use disorders and major depression were 0.73, 0.80, and 0.65, as determined from an independent test-retest study conducted in a general population sample (Grant et al. 1995).

Alcohol and Drug Treatment

Respondents in the survey were asked if, during the past year, they had gone anywhere or seen anyone for problems related to their drinking. To

more completely capture the entire alcohol help-seeking population, respondents were specifically instructed to indicate any help they had received for their drinking, including help for combined alcohol and drug use if alcohol was the major problem for which they sought help. Alcohol treatment sources were defined broadly and respondents were asked to indicate separately whether they sought help from 23 different treatment sources: inpatient alcohol and/or rehabilitation programs and inpatient wards of general or psychiatric hospitals; outpatient clinics and alcohol and/or drug detoxification units; 12-step groups including Alcoholics Anonymous, Narcotics or Cocaine Anonymous, or Alanon; social services; and various health professionals such as psychiatrists, psychologists, social workers, and the clergy. Respondents receiving help from any of these sources during the past year constituted the alcohol treatment group examined in this study. The drug treatment measure included the same range of treatment sources as described for alcohol, but information was solicited from respondents regarding help they had received for a drug problem, including help for combined drug and alcohol use if use of a drug or drugs was the major problem for which they sought help.

RESULTS

Tables 1 and 2 separately present the population estimates and prevalence of individuals with past year alcohol and drug use disorders by comorbidity and treatment status. The most striking finding in these tables is the extremely low prevalence of alcohol and drug treatment among those classified with an alcohol or drug use disorder, respectively. Only 1,365,111 (9.9 percent) of the 13,759,846 Americans with alcohol abuse or dependence in the past year sought treatment. Among the 2,855,751 Americans with a past-year drug use disorder, 8.9 percent (N = 253,611) sought treatment for a drug problem.

As shown in table 1, the percentage of respondents with alcohol use disorders seeking alcohol treatment approximately doubled when a comorbid drug use disorder (from 7.8 to 14.9 percent) or a comorbid major depression (from 7.8 to 16.9 percent) was present. The corresponding percentage was four times as great (35.3 percent) when both a comorbid drug use disorder and major depression were present compared to when they were absent (7.8 percent). The percentage of respondents seeking drug treatment with no comorbid disorder (8.6 percent) was greater than those with an additional alcohol

TABLE 1. *Number and percentage of respondents with an alcohol use disorder by comorbidity and treatment status: United States, 1992.*

Comorbidity status	No alcohol treatment	Alcohol treatment		
	N	N	Percent	(SE)
Any alcohol dx (no MDD/no drug dx)	10,141,815	857,915	7.80	(0.68)
Alcohol abuse (no MDD/no drug dx)	4,573,922	199,168	4.17	(0.73)
Alcohol dependence (no MDD/no drug dx)	5,567,893	658,747	10.58	(1.03)
Any alcohol dx (no MDD/any drug dx)	1,223,770	213,373	14.85	(2.24)
Alcohol abuse (no MDD/any drug dx)	445,763	18,829	4.05	(2.13)
Alcohol dependence (no MDD/any drug dx)	778,007	194,544	20.00	(3.10)
Any alcohol dx (MDD/no drug dx)	782,098	159,099	16.90	(2.85)
Alcohol abuse (MDD/no drug dx)	281,788	29,245	9.40	(3.71)
Alcohol dependence (MDD/no drug dx)	500,310	129,854	20.61	(3.65)
Any alcohol dx (MDD/any drug dx)	247,052	134,724	35.29	(5.99)
Alcohol abuse (MDD/any drug dx)	79,547	0	0.00	(0.00)
Any alcohol dependence (MDD/any drug dx)	167,505	134,724	44.58	(7.09)
Totals	12,394,735	1,365,111	9.92	-0.59

KEY: MDD = Major depressive disorder.

TABLE 2. *Number and percentage of respondents with a drug use disorder by comorbidity and treatment status: United States, 1992.*

Comorbidity status	No drug treatment	Drug treatment		
	N	N	Percent	(SE)
Any drug dx (no MDD/no alcohol dx)	807,981	76,448	8.64	(1.88)
Any drug abuse (no MDD/no alcohol dx)	616,522	36,230	5.55	(1.98)
Any drug dependence (no MDD/no alcohol dx)	191,459	40,218	17.36	(4.25)
Any drug dx (no MDD/any alcohol dx)	1,355,859	81,284	5.66	(1.31)
Any drug abuse (no MDD/any alcohol dx)	1,010,822	11,854	1.16	(0.77)
Any drug dependence (no MDD/any alcohol dx)	345,037	69,430	20.00	(3.85)
Any drug dx (MDD/no alcohol dx)	128,345	24,058	16.90	(5.29)
Any drug abuse (MDD/no alcohol dx)	73,315	6,580	9.40	(3.98)
Any drug dependence (MDD/no alcohol dx)	55,030	17,478	20.61	(5.09)
Any drug dx (MDD/any alcohol dx)	309,955	71,821	35.29	(6.24)
Any drug abuse (MDD/any alcohol dx)	188,530	25,826	0.00	(5.10)
Any drug dependence (MDD/any alcohol dx.)	121,425	45,995	44.58	(7.68)
Totals	2,602,140	253,611	8.88	(1.32)

KEY: MDD = Major depressive disorder.

use disorder (5.7 percent). However, the presence of a comorbid major depression with (15.8 percent) or without (18.8 percent) a comorbid alcohol use disorder nearly doubled the percentage of respondents with drug use disorders seeking drug treatment compared to those with no comorbidity. Not surprisingly, the percentage of respondents seeking treatment for an alcohol use disorder was greater when the comorbid drug use disorder was abuse than when it was dependence. A similar trend was observed for comorbid alcohol use disorders among respondents classified with a drug use disorder who sought treatment during the past year.

Tables 3 and 4 present the past-year prevalence of individuals with past-year alcohol and drug use disorders by comorbidity status and specific type of treatment facility. Although the percentage of respondents seeking help from 12-step group programs and inpatient and outpatient facilities increased as a function of comorbidity status, help seeking for an alcohol use disorder in each type of facility increased twofold in the presence of a drug use disorder, threefold in the presence of a comorbid major depressive disorder, and fivefold in the presence of both comorbidities. In contrast, help seeking for a drug use disorder decreased in the presence of an additional comorbid alcohol use disorder, but increased 30 percent or remained unchanged in the presence of a comorbid major depressive disorder, and increased 30 to 51 percent in the presence of both comorbid conditions.

Among respondents with alcohol use disorders and comorbid drug use disorders, help was sought more often from 12-step group programs, while outpatient services were more often sought when a comorbid major depressive disorder was involved. For respondents with drug use disorders, help seeking from 12-step group programs and outpatient services were equally likely regardless of comorbidity status.

DISCUSSION

The major findings of this study show that comorbid substance use disorders and major depressive disorder have a major impact on obtaining treatment for an alcohol or drug use disorder regardless of type of treatment facility. In general, respondents with past-year alcohol use disorders were twice as likely to seek help for their alcohol problems in the presence of either a comorbid drug use disorder or a major depression,

TABLE 3. *Percentage of respondents in alcohol treatment by comorbidity and treatment status: United States, 1992.*

Comorbidity status	12-step group	Inpatient	Outpatient	Any treatment
Any alcohol dx (no MDD/no drug dx)	5.4	2.7	4.6	7.8
Alcohol abuse (no MDD/no drug dx)	2.3	1.0	1.9	4.2
Alcohol dependence (no MDD/no drug dx)	7.8	3.9	6.7	10.6
Any alcohol dx (no MDD/any drug dx)	10.8	6.5	9.9	14.9
Alcohol abuse (no MDD/any drug dx)	1.7	1.1	1.2	4.1
Alcohol dependence (no MDD/any drug dx)	15.1	9.0	14.1	20.0
Any alcohol dx (MDD/no drug dx)	10.7	9.1	12.2	16.9
Alcohol abuse (MDD/no drug dx)	7.7	1.4	3.1	9.4
Alcohol dependence (MDD/no drug dx)	12.2	12.9	16.6	20.6
Any alcohol dx (MDD/any drug dx)	20.8	16.8	27.4	35.3
Alcohol abuse (MDD/any drug dx)	0.0	0.0	0.0	0.0
Alcohol dependence (MDD/any drug dx)	26.3	21.2	34.7	44.6

KEY: MDD = Major depressive disorder.

TABLE 4. *Percentage of respondents in drug treatment by comorbidity and treatment status: United States, 1992.*

Comorbidity status	12-step group	Inpatient	Outpatient	Any treatment
Any drug dx (no MDD/no alcohol dx)	6.0	3.3	7.2	8.6
Any drug abuse (no MDD/no alcohol dx)	3.0	2.2	4.6	5.6
Any drug dependence (no MDD/no alcohol dx)	14.5	6.5	14.5	17.4
Any drug dx (no MDD/any alcohol dx)	4.6	4.4	3.9	5.7
Any drug abuse (no MDD/any alcohol dx)	0.5	0.9	0.0	1.2
Any drug dependence (no MDD/any alcohol dx)	14.9	12.9	13.6	16.8
Any drug dx (MDD/no alcohol dx)	8.4	3.0	10.4	15.8
Any drug abuse (MDD/no alcohol dx)	7.5	0.0	0.7	8.2
Any drug dependence (MDD/no alcohol dx)	9.4	6.3	21.1	24.1
Any drug dx(MDD/any alcohol dx)	12.3	6.0	10.4	18.8
Any drug abuse (MDD/any alcohol dx)	9.6	2.5	2.5	12.1
Any drug dependence (MDD/any alcohol dx)	15.8	10.6	20.6	27.5

KEY: MDD = Major depressive disorder.

and five times more likely to seek help when both comorbidities were present. In contrast, a comorbid alcohol use disorder alone did not increase help seeking among respondents with past-year drug use disorders, while help seeking increased twofold for these respondents when a major depressive disorder was present with or without a comorbid alcohol use disorder. These results, in combination, suggest that the severity of an alcohol or drug use disorder may be greater in the presence of a comorbid major depression, thereby increasing help-seeking behaviors. Moreover, the results indicate that the magnitude of the association often cited between substance use disorders and major depression in treated samples may be artificially inflated. That is, this association may represent the greater propensity of respondents with comorbid major depression to seek treatment for a substance use disorder compared to those individuals with no comorbid major depression.

Perhaps one of the most interesting results of this study is the sheer number of respondents with alcohol and drug use disorders missing from the treated population. Only 9.9 percent and 8.8 percent of the respondents classified with past-year alcohol or drug use disorders, respectively, sought treatment. The percentages of respondents not seeking treatment are much lower than the corresponding percentage reported in other general population surveys. For example, in the Epidemiologic Catchment Area (ECA) survey, 21 percent of the respondents with an alcohol use disorder sought treatment while 28 percent of the respondents with a drug use disorder did so during the year preceding the interview (Narrow et al. 1993). The examination of the reasons the majority of individuals with substance use disorders do not seek treatment, regardless of comorbidity status, would require a more indepth analysis of factors impacting on help seeking than is possible here. Future studies using the present survey data will address this important unexplored issue.

This study helped to answer the fundamental question of whether the association between substance use disorders and major depression observed in clinical settings is artifactual, that is, a function of increased treatment seeking. The findings suggest that the magnitude of the association between substance use disorders and major depression seen in clinical samples is, in part, due to increased treatment-seeking behavior in comorbid individuals. However, it remains unclear whether increased treatment seeking among comorbid individuals is the result of the increased severity of the substance use disorder due to comorbid major depression or of other factors not examined here. Future analyses of the survey data will explore the numerous factors influencing treatment entry,

including a full array of sociodemographic variables, enabling variables (e.g., income, availability to health insurance coverage), and need factors that impact on the severity level of both comorbid disorders.

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Challenges in Assessing Substance Use Patterns in Persons With Comorbid Mental and Addictive Disorders

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Assessment of substance use patterns can be distinguished from two related assessment goals. These consist of screening (i.e., identifying persons with addiction problems) and diagnosis (i.e., determining whether abuse or dependence criteria are met). All three goals are important and relevant to persons with comorbid disorders. Nonetheless, this chapter focuses on substance use assessment for three reasons. One, it is the least studied assessment goal in the comorbidity literature; very few published studies address this topic. Two, substance use assessment is applicable to all persons in treatment for mental disorders. Use of illicit drugs or alcohol is more common than abuse, and information about use patterns may be desired to determine risk for medication-drug interactions and other health concerns. Finally, substance use assessment should play a central role in the treatment of comorbid disorders. It serves as the basis for treatment planning and as a point of departure for outcome assessment. It also constitutes the first step in conducting a functional analysis of drinking and/or drug use for an individual (Sobell et al. 1988). Quantifying patterns of substance use allows for determination of increased versus decreased use, an outcome measure consistent with harm reduction approaches to treatment of substance misuse in the context of major mental disorders (Carey, in press).

In the addictions literature, a rich tradition of research exists on topics related to assessing alcohol and drug use patterns. Ample sets of instruments and guidelines for their use have been developed and standardized in substance abuse treatment settings. However, importing such tools for use with persons with major mental disorders raises questions about their psychometric properties and other potential limitations. This chapter briefly summarizes current approaches to, and problems with, substance use assessment. Because self-report measures continue to be widely used, emphasis is placed on factors generally considered to affect the accuracy of self-reported substance use. Next, concerns about the reliability and validity of self-reported substance use

in persons with major mental disorders are discussed. Finally, recommendations for enhancing the reliability and validity of assessment instruments are presented, highlighting areas in need of empirical research.

CURRENT APPROACHES TO SUBSTANCE USE ASSESSMENT

To borrow a scheme used by Skinner (1984), options available for substance use assessment include (a) prospective methods, (b) retrospective methods, and (c) objective indicators. Prospective methods consist of variants on self-monitoring. Self-monitoring reduces reliance on memory, and is generally regarded as the most accurate alternative to direct observation. Successful self-monitoring does, however, require a subject with the skills and motivation to complete the task. Prospective information gathering also requires time. Retrospective methods involve asking the subject to report on past substance use over a designated time interval. Examples include the Addiction Severity Index (ASI) (McLellan et al. 1980), the Time Line Follow-back interview (TLFB) (Sobell and Sobell 1992), and various quantity-frequency methods (e.g., Cahalan and Room 1974; Polich et al. 1981). Retrospective self-report is practical for most settings and is the most frequently used. However, its drawbacks include the potential for memory failure or other sources of distortion. Objective indicators include blood- or urine-based drug screens, breathalyzer tests, laboratory tests (e.g., gamma-glutamyl transpeptidadase, high density lipoproteins, mean corpuscular volume), collateral reports, and official records. Each of these information sources has limitations. Breathalyzer tests and blood/urine screens yield information about recent use only (Schwartz 1988). Other laboratory tests identify medical consequences of substance use, but are generally sensitive only to prolonged high levels of use; furthermore, elevations are nonspecific to substance use. None of these indices yields data on the pattern of substance use. Collateral reports or other official records tend to be limited due to incomplete knowledge or representation of actual use history, and collaterals may be unavailable for some socially isolated subjects (Drake et al. 1993; O'Farrell et al. 1984).

In the absence of a gold standard, confidence in the accuracy of assessment can be enhanced by adopting a convergent validity approach (Sobell and Sobell 1980). This involves using multiple indicators that will tend to converge on a consistent picture of actuality. Significant discrepancies must be evaluated from a methodological perspective as

well as allowing for subject-specific factors. In any given population, consideration must be given to appropriate selection of measures as well as to ways in which their accuracy can be enhanced. Since retrospective self-reports continue to serve as the cornerstone of assessment, factors affecting the validity of self-reported substance use will be considered next.

Factors Affecting Validity of Self-Reported Substance Use

For substance use assessment to be useful in a treatment context, measures must be both accurate and sensitive to change. The literature on accuracy indicates that acceptable levels of reliability and validity are found for alcoholics' self-reports when recommended procedures are followed (e.g., O'Farrell and Maisto 1987; Sobell and Sobell 1980). However, some samples and procedures have yielded less than impressive findings. Furthermore, the reliability and validity of self-reported drug use varies across both studies and types of drugs (Maisto et al. 1990). Test-retest reliability is infrequently reported and, when it is, shows only modest reliability coefficients. Validity coefficients tend to be similarly moderate. A reasonable conclusion is that self-report data are "inherently neither valid nor invalid, but vary with the methodological sophistication of the data gatherer and the personal characteristics of the respondent" (Babor et al. 1990, p. 8).

In the substance abuse field, questions have thus moved beyond "Are self-reports valid?" and are framed more as "When, and under what conditions, are self-reports valid?" (Brown et al. 1992). It is this approach to evaluating the accuracy of self-reports that provides a framework for understanding the process of substance use assessment among persons with major mental disorders.

In a discussion of the factors affecting the accuracy of self-reported substance use, Babor and colleagues (1990) highlighted four classes of variables. The first class yields characteristics of the respondent. These include the respondent's state of sobriety at the time of assessment and the possible influence of a social desirability response set. The second class of variables includes aspects of the task that might enhance or detract from accurate responding. These include the degree of rapport between assessor and respondent, whether assurances of confidentiality can be made, the likelihood that self-reports will be verified, the criterion interval reported on, and the clarity of the questions. Motivational factors constitute the third class of variables affecting accuracy of self-report. Obvious short-term goals (e.g., to obtain treatment or to avoid arrest)

must be considered, as well as the fear of potentially judgmental attitudes or other threats to the respondent's self-esteem. Cognitive processes constitute the fourth type of variables influencing self-report accuracy. Impairment of attentional processes, verbal comprehension, or retrieval will interfere with the accuracy of an assessment. Cognitive processes may be impaired due to recent alcohol or drug use, to situational stress or anxiety, or to associated psychiatric syndromes such as depression. In addition, recall of past behavior is subject to information-processing biases, so that recall is disproportionately influenced by salient and/or very recent events.

Application to Persons With Severe Mental Disorders

There are reasons for concern about the reliability and validity of substance use assessment in persons with severe mental disorders (e.g., schizophrenia, bipolar disorder, major depressive disorder). Several studies suggest significant underreporting of substance abuse in this population (e.g., Safer 1987; Shaner et al. 1993; Test et al. 1989). No formal reliability or validity studies have been published on substance use assessment, but the accuracy of screening measures has been empirically addressed. For example, the criterion validity of screening measures (e.g., the Michigan Alcoholism Screening Test) has been evaluated in psychiatric settings. Results indicate adequate sensitivity but low specificity (Drake et al. 1990; Teitelbaum and Carey, in press), suggesting that population differences may affect the psychometric properties of many of the standard industry tools. A recently completed literature review (Teitelbaum and Carey, in press) found surprisingly few studies addressing the reliability of alcohol/drug screening or diagnostic measures used with psychiatric patients. In this population, which is characterized by fluctuating mental status, the issue of test-retest stability is a fundamental psychometric concern.

Clinical characteristics of persons with major mental disorders offer many potential sources of unreliability and/or invalidity. For example, in an emergency room setting, Barbee and associates (1989) found that significant numbers of schizophrenic patients were unable or unwilling to complete structured interviews. The presence of acute psychotic symptoms can impair reality orientation, thus invalidating responses. Common correlates of mental disorders such as hostility and psychosocial instability raise concerns about compliance and cooperativeness with assessments. Interactive effects of recent substance use, psychiatric symptoms, and prescribed medications increase the risk of cognitive

impairment. In addition, some persons with mental disorders report concerns about the impact of accurate reporting on their psychiatric treatment. Fears about losing access to medications or being transferred to another facility may motivate underreporting of substance use (Ridgely et al. 1990). Finally, anxiety about further stigmatization because of multiple disorders may come into play.

Such clinical concerns suggest that important variables may include (a) the setting in which the assessment takes place (e.g., emergency room versus community mental health center); (b) the timing of the assessment (on admission versus later in treatment); and (c) institutional policies on providing integrated versus separated treatment. However, empirical data to evaluate these possibilities are unavailable. Clearly, there is a need for procedures paralleling the efforts by researchers in mainstream substance abuse settings to document the respondent, task, motivational, and cognitive factors that might affect the reliability and validity of self-reports in mental health settings. At the present time, however, even preliminary demonstrations supporting the accuracy of self-reported substance use patterns are lacking.

STATUS OF EMPIRICAL LITERATURE ON SUBSTANCE USE ASSESSMENT IN THIS POPULATION

Data from an ongoing study provide preliminary evaluations of the concurrent validity of self-reported alcohol and/or drug use. The subjects are outpatients at a state psychiatric center in a medium-sized city in upstate New York; all are voluntary participants in a longitudinal investigation of the psychosocial aspects of functioning of persons with severe mental disorders. The data provide information on the extent of agreement between self-reported substance use (obtained from the ASI) and information provided by collateral reports and urinalysis results, and also allow comparison of the concordance between self-reported drinking on two separate measures. Finally, the TLFB is evaluated with respect to known groups' validity.

ASI and Collaterals

Forty-five subjects provided data for this analysis. All were outpatients, three-quarter had been given schizophrenia-spectrum diagnoses, and one-quarter had been diagnosed with bipolar disorders. Most were male (84 percent), and 92 percent received pensions for a psychiatric disability.

Each subject identified a collateral who could provide information about the subject's substance use and other functioning. Collaterals were interviewed over the phone within a few days of an interview with the subject. A third of the collaterals interviewed were in daily contact with subjects, a third saw subjects weekly, and another third saw subjects at least once during the target month. Friends (often fellow patients) and treatment/residential staff were most often identified as collaterals.

For 10 substance use categories, subjects were asked how many days in the past 30 they had used the substance, following standard ASI interview procedures. The collaterals were asked, "To the best of your knowledge, did (insert subject's name) use this substance in the last 30 days?" To make responses comparable, subjects' estimates of frequency were collapsed into a simple use/no use index.

As shown in table 1, six categories were endorsed; for these the percentages of agreement ranged from 84 to 98, primarily due to the high levels of agreement that no use occurred. Inspection of the kappa coefficients (Cohen 1960) indicates no association above that expected for chance in the majority of drug categories.

Subjects admitted 24 instances of substance use, which included multiple use by single subjects, but collaterals were able to corroborate subjects' recent use history accurately in only 7 instances. In the other

TABLE 1. *Concordance between self-report and collateral report of use in the past 30 days.*

Substance	ASI / Collateral	- -	+ +	+ -	- +	% agreement	kappa
Alcohol--any use		36	4	5	0	89	0.56
Alcohol--to drunkenness		38	0	7	0	84	0.00
Marijuana		42	3	2	0	96	0.75
Benzodiazepines		46	0	1	0	98	0.00
Cocaine		46	0	1	0	98	0.00
Amphetamines		46	0	1	0	98	0.00

KEY: "+" = a positive report of use; "-" = a negative report of use (i.e., no use in the past month).

17 instances, subjects reported more use than did the collateral. These findings are consistent with previous research on collateral verification in nonpsychiatric samples that has found a tendency towards underreporting by collaterals (O'Farrell and Maisto 1987). The nature of the collaterals identified by subjects confirms suspicions that, for many mentally ill persons, a collateral who is both reliable and knowledgeable about substance use may be unavailable (Drake et al. 1993). Notably, however, there were no cases where collaterals alerted the author to substance use that subjects did not report. The nature of subject sample undoubtedly accounts in large part for the lack of surprises; subjects were psychiatrically stable, most were engaged in treatment, and their sobriety at the time of assessment was documented. Thus, during the course of the research interviews, it was possible to follow many of the recommended procedures presented later in this chapter.

ASI and Urinalysis

The results of urine tests were also used for validation. It is important to keep in mind that the time spans of these measures differ (i.e., the ASI addresses the past 30 days, and urine tests are usually sensitive only to a few days), making urine tests imperfect methods for confirming self-reports of substance use patterns over an extended period. However, the major concern was the occurrence of negative self-reports and positive urine test results, which would indicate underreporting of even salient recent use.

Both kinds of data were available for 53 outpatients. Table 2 shows percentages of agreement and kappa coefficients for the seven categories of substances that yielded positive findings. The lowest agreement rates were obtained for alcohol and marijuana, which many subjects admitted to using but which were not picked up on urinalysis. Of the six positive urines obtained, three were not substantiated by self-report (two for cocaine and one for barbiturates). Thus, even a relatively insensitive validation tool gave reason to suspect underreporting of some drugs. These findings need to be replicated, especially in samples with higher base rates for substance use.

Concurrent Self-Reports

Evaluation of the concurrent validity evidence for self-reported frequency of alcohol use was also possible, using data from both the ASI alcohol

TABLE 2. *Concordance between self-report and urinalysis.*

Substance	ASI / Urinalysis	- -	+ +	+ -	- +	% agreement	kappa
Alcohol		41	0	12	0	77	0.00
Marijuana		45	1	7	0	87	0.23
Cocaine		50	1	0	2	96	0.43
Amphetamines		52	0	1	0	98	0.00
Barbiturates		52	0	0	1	98	0.00
Benzodiazepines		51	1	1	0	98	0.66
Narcotics		52	0	1	0	98	0.00

KEY: "+" = confirmation of use (by self-report or urinalysis result);
"-" = no self-report of use or two negative urinalysis results.

section and the TLFB procedure. Both yield estimates of the number of days the subject drank in the past 30. Techniques for eliciting this information vary, however. The ASI asks for the number of drinking days during the past 30 as a single question, whereas the TLFB presents the visual prompt of a calendar, and uses numerous other memory prompts to elicit daily drinking information (see Sobell and Sobell 1992).

To repeat, subjects were adult psychiatric outpatients, predominantly male (83 percent) with schizophrenic-spectrum diagnoses (75 percent). These tend to be a chronically dysfunctional group; none were employed full-time, and 92 percent were psychiatrically disabled. Overall, the correlation between the two measures of alcohol use was 0.75 ($p < 0.0001$); figure 1 gives a graphic display of the relationship. In 39 of 52 assessments (75 percent), no drinking was reported on both measures. Only three of 52 denied drinking on one measure but admitted to drinking on the other, and, in all three cases, the TLFB identified drinking days when the ASI did not. In 10 of the 13 instances in which drinking was reported (77 percent), the drinking was identified on both measures. In seven cases, more drinking days were reported on the TLFB; the opposite was true in only three cases.

These data suggest that the TLFB strategy may yield higher estimates of drinking than the ASI, at least over a 30-day interval. This finding may be explained by the structure of the interview, because the TLFB uses

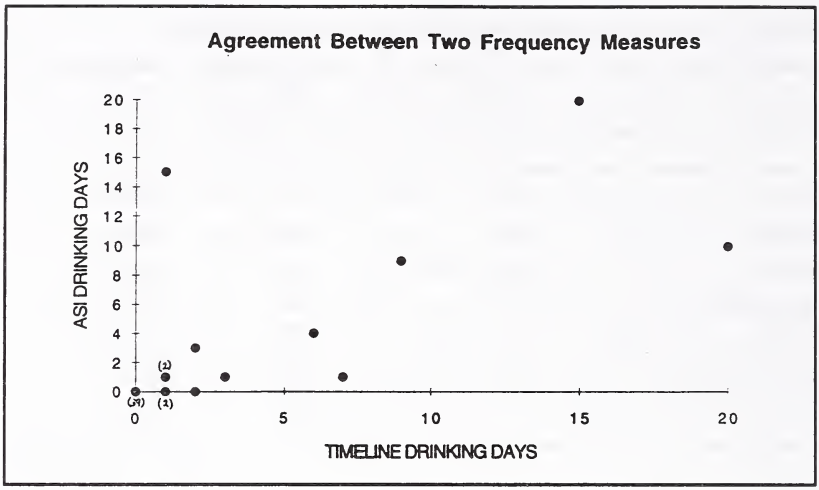

FIGURE 1. *Agreement between two frequency measures.*

multiple verbal and visual prompts for recalling events that might be associated with drinking. However, the potential advantages of the TLFB strategy should be weighed against its potential limitations. Although it may be more accurate, it is also more time consuming. The accuracy of TLFB assessments covering more than 30 days should also be explored in order to determine representative baselines. In any case, differences between methods of eliciting alcohol use information with chronically mentally ill subjects should be evaluated further.

Known-Groups Validity

Finally, this research yields data that permit a preliminary validation of the TLFB on known groups. Of 64 outpatients who were evaluated with the SCID and who completed a 6-month TLFB, 13 qualified for an alcohol abuse or dependence diagnosis in the past 6 months; these are labeled abusers in table 3. Abusers reported significantly fewer abstinent days and consistently more drinking days in the past 6 months than nonabusers. Unequal variances for light, moderate, and heavy drinking days account for the absence of significant group differences on these variables. Abusers also reported significantly greater maximum quantities (in numbers of standard drinks) consumed on a single day.

Similarly, primary therapists rated subjects on the Case Manager Rating Scale (Drake et al. 1990), an ordinal scale developed and validated by

TABLE 3. *Self-reported alcohol use by subjects grouped according to abuse/dependence status.*

	Self-reported alcohol use from timeline follow-back				
SCID alcohol abuse or dependence status	Abstinent days*	Light days	Moderate days	Heavy days	Maximum quantity**
Nonabusers (N = 51)	172.51	3.76	1.51	2.23	2.08
Abusers (N = 13)	132.61	17.31	10.77	19.31	9.69

KEY: * = $p < 0.05$; ** = $p < 0.001$; SCID = Structural Clinical Interview for DSM-III-R.

Drake and colleagues that reflects the following degrees of alcohol use over the previous 6 months: no use, mild use but no problems, moderate use with some resulting problems, severe problems, and extremely severe problems probably resulting in hospitalization. All but one subject received ratings in the first three categories, so that only the 63 subjects assigned to the no use, mild, and moderate use categories were used for analysis. As shown in table 4, subject-generated TLFB data covering the same 6-month interval seem to be consistent with therapists' ratings. While finding predictable group differences on a measure does not indicate an accurate reflection of reality, it does suggest that subjects who are perceived by professionals as having more alcohol involvement do report more nonabstinent days and heavier alcohol consumption.

Enhancing the Accuracy of Substance Use Assessment

By integrating the above data and the literature (see Drake et al. 1993; Nurco 1985; Skinner 1984; Sobell and Sobell 1980), it is possible to offer several recommendations for enhancing the accuracy of substance use assessment among persons with major mental disorders. These are organized below according to the four-factor scheme presented earlier.

TABLE 4. *Self-reported alcohol use by subjects groups according to therapists' ratings.*

	Self-reported alcohol use from timeline follow-back				
Case manager rating scale determination	Abstinent days[a]	Light days	Moderate days	Heavy days[b]	Maximum quantity[c]
No use of alcohol (N = 35)	178.00	0.83	1.17	0.05	1.49
Mild use, no problems (N = 17)	159.71	10.29	2.35	8.64	4.29
Moderate use, some problems (N = 11)	124.67	22.56	5.89	26.89	12.44

KEY: a = $F(2,55) = 10.77$, $p < 0.0001$; moderate use < mild use and no use; b = $F(2,55) = 6.62$, $p < 0.003$; moderate use > no use; c = $F(2,55) = 13.50$, $p < 0.0001$; moderate use > mild use and no use.

Respondent Characteristics

- Assess when the subject is psychiatrically stable. Available evidence suggests that less accurate reports are likely to be obtained on admission interviews or in more acute care settings (e.g., Barbee et al. 1989; Shaner et al. 1993) than among stable outpatients. Even in the absence of an underreporting bias, impairment in reality testing may have unpredictable effects on self-reported substance use patterns. The conditions under which psychotic symptoms impair self-report accuracy remain to be documented empirically.

- Assess when the subject is not intoxicated or in withdrawal. Many studies of primary substance abusers have found less accurate reporting when subjects were intoxicated (e.g., Brown et

al. 1992). This finding should also generalize to mentally ill substance abusers. Another lesson from the substance abuse literature suggests using objective measures of intoxication (i.e., breath or urine tests), because even trained interviewers are not always able to detect intoxicated individuals (Sobell et al. 1979).

Motivation

- Use self-report in conjunction with other sources of information (lab tests, collaterals), and tell subjects that self-report will be checked against other sources. This convergent validity approach to substance use assessment (Sobell and Sobell 1980) enhances confidence in the validity of self-reports when sources converge and identifies discrepancies when they diverge. In this research, subjects know from the time of informed consent that breath and urine tests will be performed and that collaterals will be called. Although it is not possible to empirically test the effects of these procedures on the accuracy of self-reports in a mental health setting, this common procedure should reduce the likelihood of deliberate underreporting.

- Provide assurances of the confidentiality of the data, when possible.

- Evaluate whether the subject has reasons for distorting his or her reports, and address those motivational factors. Common concerns include losing access to medications, change in treatment site, or legal ramifications if the full extent of substance use is known. It is likely that fully integrating substance abuse treatment into mental health treatment will reduce both the motivation to compartmentalize symptoms and the fear that honesty about substance use will complicate ongoing treatment.

Task Variables

- Conduct substance use assessment after assessing other areas of life functioning and history. This sequence helps to build rapport and raises the interviewer's awareness of the subject's competencies and limitations that can assist in the interpretation of self-report data. Of relevance here is the frequent finding that alcoholics give less reliable and valid information at pretreatment

assessments than during treatment or posttreatment assessments (Skinner 1984). This suggests that the degree of rapport and/or trust developed over time influences subjects' willingness to accurately report alcohol or drug use.

- Use nonjudgmental interviewers who are comfortable with the vocabulary of substance use and familiar with substance use patterns.

- Use simple, direct questions and clearly defined timeframes. This research focuses on frequency rather than on quantity, which can be more difficult to specify. However, the author's data suggest that maximum number of drinks consumed on a single day distinguishes those who experience drinking problems and those who do not.

As for timeframes, the author has found that focusing on substance use over the last month has worked well. In this population, use patterns tend to vary over time, interrupted by changes in functional abilities, hospitalizations, or constrained by financial limitations. Such irregular patterns of use tend to be harder to describe than very regular use, especially with averaged quantity-frequency methods. The utility of timeline assessments over varying intervals should be explored.

- Use open-ended questions and normalize substance use to make it more likely that subjects will admit to heavier quantities and greater frequencies when relevant. As pointed out by Babor and colleagues (1990), people tend to avoid extremes when fixed options are provided. Framing the questions in a way that normalizes a wide range of use patterns yields a wider range of reports; an example is "Many people have experimented with drugs in their lives . . . which of the following have you had experience with . . . " The majority of severely mentally ill outpatients report extensive drug histories, even though minimal information may be available in the medical chart. This suggests that there are effective and ineffective methods for eliciting such information.

Cognitive Processes

- Use the lowest level of specificity or precision consistent with meeting assessment goals. A certain level of specificity is needed

to ensure that data are useful for treatment planning and evaluation of change. However, among persons with major mental illnesses, requests for highly specific descriptions of past behavior can be daunting and result in questionably valid responses. Even in the general population, global measures tend to be more valid than specific measures when assessing drug use (Harrell 1985); this pattern may be especially true for persons with comorbid disorders. Thus, researchers must strike a balance between obtaining data that are valid and yet still useful to meet specific assessment goals. The nature of this balance requires study as clinical research efforts begin to include substance use patterns in outcome assessments among persons with major mental illnesses.

- Incorporate repeated assessments over time whenever possible, taking a longitudinal approach to substance use assessment. This recommendation addresses both cognitive and task concerns. Experience with drug use surveys indicates that recent events are recalled more clearly than remote ones (Harrell 1985), so that frequent assessment over short intervals minimizes dependence on subjects' memories. In addition, direct observations about the psychosocial impact of substance use by staff or other collaterals can supplement reports of recent behavior. Integration of multiple sources of information has been recommended as an effective method of enhancing accuracy of substance use assessment (Drake et al. 1990; Sobell and Sobell 1980). Finally, as mentioned earlier, use patterns in this population tend to vary substantially over time, so that obtaining a representative baseline may require an extended assessment period.

ESTABLISHING A RESEARCH AGENDA

The preceding review identifies several directions for future research. First, basic information on the temporal stability of self-reported substance use patterns among persons with co-occurring mental and addictive disorders is needed. Second, empirical investigation of the effects of various task variables on the accuracy of self-reported substance use patterns should be undertaken. Relevant variables include the format of the measurement tools (e.g., ASI versus TLFB) and the timeframes employed. Third, it is important to investigate ways of minimizing the impact of respondent and cognitive limitations. In

addition to drug-related cognitive impairment, attention must be paid to those aspects of psychopathology that can reduce self-report accuracy and the interaction between the two. Fourth, it would be beneficial to understand the kinds of motivational variables that might distort self-report in this population. Ultimately, these factors will allow a better answer to the question: When and under what conditions are self-reports of substance use valid for persons with major mental disorders?

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Anxiety Disorders, Comorbid Substance Abuse, and Benzodiazepine Discontinuation: Implications for Treatment

David H. Barlow

INTRODUCTION

Comorbidity among various disorders complicates research and practice. Comorbidity among emotional disorders and substance use disorders is a particularly thorny problem due to the dearth of relevant clinical research. This chapter reviews what is known about the comorbidity of substance use and anxiety disorders and presents recent data collected in the context of comorbid anxiety and mood disorders that may have implications for the relationship of anxiety and substance use disorders. The specific case of the relationship of benzodiazepine use to successful outcome of psychosocial treatments and recent developments in successful psychosocial strategies for discontinuing benzodiazepines in anxious patients may provide important information for future studies. This chapter begins with a brief review of data on the co-occurrence of substance use and anxiety disorders.

COMORBIDITY AMONG SUBSTANCE USE AND ANXIETY DISORDERS

A number of studies have reported a high rate of comorbidity among anxiety and substance use disorders. Most of these studies have surveyed alcohol dependence and abuse. Rates of comorbidity have typically been calculated in two different ways. First, the prevalence of anxiety disorders has been examined in alcohol dependence and abuse patient samples. Second, rates of alcohol dependence and abuse have also been examined in samples of outpatients with anxiety disorders.

The majority of surveys have followed the first approach and have found that the lifetime prevalence of clinically significant anxiety disorders in patients with alcohol abuse and dependence ranges from 25 percent to 45 percent for patients with clearly defined anxiety disorders, but may

approach 60 percent if one includes identifiable anxiety disorders that are subthreshold in terms of severity (Bowen et al. 1984; Chambless et al. 1987; Hesselbrock et al. 1985; Mullaney and Trippett 1979; Smail et al. 1984; Cox et al. 1989; Johannessen et al. 1989).

Surveys using the second approach and examining rates of alcohol dependence and abuse in anxiety disorder outpatient samples suggest that approximately 15 percent to 25 percent present with evidence of current or past alcohol abuse or dependence (Bibb and Chambless 1986; Thyer et al. 1986). Himle and Hill (1991) found that the frequency of alcohol abuse or dependence differed among persons with various anxiety disorders. For example, the percentage of alcohol abuse or dependence among those individuals with a principal diagnosis of panic disorder (PD) with agoraphobia (who may also have presented with additional anxiety disorders) was 31.5 percent, as compared to 24.6 percent for obsessive-compulsive disorder and 14.4 percent for a specific phobia. Thus, it would seem that some anxiety disorders confer a higher risk for substance abuse then others.

In any case, there is evidence that patients presenting with these comorbid pictures have more clinically severe conditions than individuals with either condition alone. Thus, there are reasons to examine factors contributing to comorbidity in this subgroup more closely.

One method of examining the possible reasons for the acquisition of comorbid disorders is to ascertain a temporal sequence in their onset. Most studies indicate that anxiety precedes alcohol abuse and dependence. This pattern would seem to confirm the frequent clinical observation that many individuals with anxiety disorders begin to abuse alcohol with the purpose of self-medicating their anxiety disorders. However, Kushner and colleagues (1990) noted that the pattern seems to hold true only for some disorders, such as PD with or without agoraphobia, social phobia, and specific phobia. For some other disorders, particularly generalized anxiety disorder (GAD) and depression, the more prevalent pattern may be the reverse; that is, substance abuse seems to contribute to the onset of GAD and depression. One possible mechanism of action here is that the individual experiences a loss of control over the substance use subsequent to addiction and develops reactive anxiety or depression.

Illicit drug use has also been reported to precipitate anxiety disorders. For example, Aronson and Craig (1986), as well as Louie and colleagues

(1989), reported a number of cases in which cocaine use and/or withdrawal from cocaine precipitated panic attacks. In these cases the resulting panic disorder continued well after the cessation of cocaine use. In fact, as many as 30 percent of patients presenting with PD have reported an onset associated with either licit or illicit drug use (Barlow 1988), with marijuana being one of the more common precipitants. Hyperventilation and other symptoms associated with withdrawal from alcohol have also been reported to trigger long-lasting PD (Weissman 1988). In cases where substance abuse seems to "trigger" anxiety disorders, clinical strategies might target the substance use first before addressing related anxiety on the chance that anxiety, to the extent that it might be related to the substance use, would concurrently remit. These clinical speculations, however, are nothing more than assumptions since little is known about the effects of targeting one disorder when treating additional comorbid disorders in an individual.

COMORBIDITY AMONG ANXIETY AND MOOD DISORDERS: IMPLICATIONS FOR COMORBID SUBSTANCE USE DISORDERS

Research from the author's anxiety disorders research clinic has produced some evidence on the effects of comorbidity among anxiety and mood disorders on treatment outcome, both short and long term. Since these results are somewhat surprising, it is possible that they may have some implications for similar comorbid patterns among anxiety disorders and substance use disorders. One recently analyzed set of data examined the impact of treatment for panic disorder using an effective cognitive-behavioral treatment (Barlow et al. 1989) on the course and outcome of generalized anxiety disorder that was not directly treated (Brown and Barlow 1992). GAD was chosen because it is the most frequently co-occurring diagnosis in patients with a principal diagnosis of PD (Moras et al., submitted). For purposes of this analysis, the comorbid presence of GAD was considered at both a clinical level of severity as well as a subclinical level of severity in which GAD was clearly identifiable but was not considered severe enough to interfere substantially with functioning. As noted in figure 1, of 68 panic disorder patients treated, 32 percent had a clinically significant GAD additional diagnosis at pretreatment, with an additional 9 percent evidencing subthreshold GAD. At posttreatment the rate of GAD above threshold declined to 9 percent, whereas subthreshold GAD increased to 16 percent

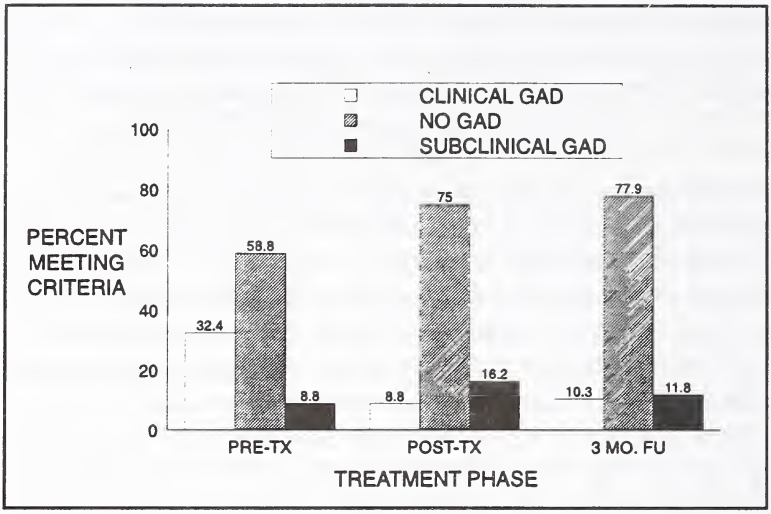

FIGURE 1. *Effects of panic control treatment on comorbid GAD diagnoses in 68 patients with panic disorder.*

KEY: Clinical GAD = Anxiety Disorders Interview Schedule-Revised [ADIS-R] diagnosis of GAD with clinical severity rating of 4 or above on a 0-8 scale; subclinical GAD = ADIS-R diagnosis of GAD with clinical severity rating below 4; PRE-TX = before treatment; POST-TX = after treatment; 3MO.FU = 3-month followup.

because several patients with a clinically significant GAD at pretreatment moved to the subclinical category at posttreatment. These results were relatively stable at a 3-month followup. Thus, in this example, a comorbid disorder improved with successful treatment of the target disorder in spite of the fact that no attempts were made to treat it directly. Of course, one possible reason for these results is that GAD and PD share many symptoms, with GAD often considered to be the "basic" anxiety disorder (Brown et al. 1994). Thus, the success-ful treatment of panic disorder may have "generalized" to symptoms comprising GAD such as anxious arousal and cognitions of future danger.

Now there is more substantial data on the impact of pretreatment and posttreatment comorbidity on outcome of treatment for panic disorder (Brown and Barlow 1995). Analyzing 87 patients with PD who completed active treatment, the investigators first looked at the effect of

the presence of additional diagnoses at pretreatment on short-term outcome (i.e., posttreatment and 3-month followup). The effect of having at least one additional diagnosis was examined on two measures of treatment outcome, high endstate status and panic-free status. Interestingly, patients with at least one additional diagnosis at pretreatment, irrespective of type, did as well at posttreatment and 3-month followup as those patients without an additional diagnosis. The presence of a mood disorder pretreatment did seem to impact somewhat on results at posttreatment, but any effect of mood disorder had disappeared by the 3-month followup; so, those PD patients with or without a mood disorder did equally well. Of more interest here is the question of whether cognitive-behavioral treatment for PD resulted in the reduction of additional diagnoses after treatment, as seemed to be the case for GAD. Fifty-three patients were utilized in these analyses because they had been administered the full assessment battery at pretreatment, 3-month followup, and 24-month followup. Basically, the results, presented in figure 2, reflect a generally improving pattern at 3-month followup in additional diagnoses, followed by a return close to baseline levels in the presence of additional diagnoses at a 2-year followup. Specifically, 39.6 percent of the patients presented with at least one additional diagnosis at pretreatment whereas 30.2 percent of the patients evidenced at least one additional diagnosis at a 2-year followup, despite the fact that these patients maintained or improved upon their treatment gains for PD symptomatology over the same interval. For example, 41.5 percent of patients met high endstate criteria in regard to their PD status at 3-month followup (a category very close to "cured"), whereas this had increased to 62.3 percent at the 2-year followup. Panic-free status remained in the 75 percent range.

Another way of examining these data is to look at the longitudinal course of additional diagnoses. For example, the five patients who were assigned a mood disorder diagnosis at the 2-year followup may or may not have been the same five patients who had a mood disorder diagnosis at pretreatment. The author and colleagues were able to make these longitudinal comparisons on 64 patients who had completed the 2-year followup. The results are presented in figure 3. As is evident in that figure, the continued presence of comorbid diagnoses was associated with poorer treatment outcome for PD at 2 years. Specifically, whereas 76.9 percent of the patients who no longer had any comorbid diagnoses met high end-state criteria, only 33.3 percent of the patients with

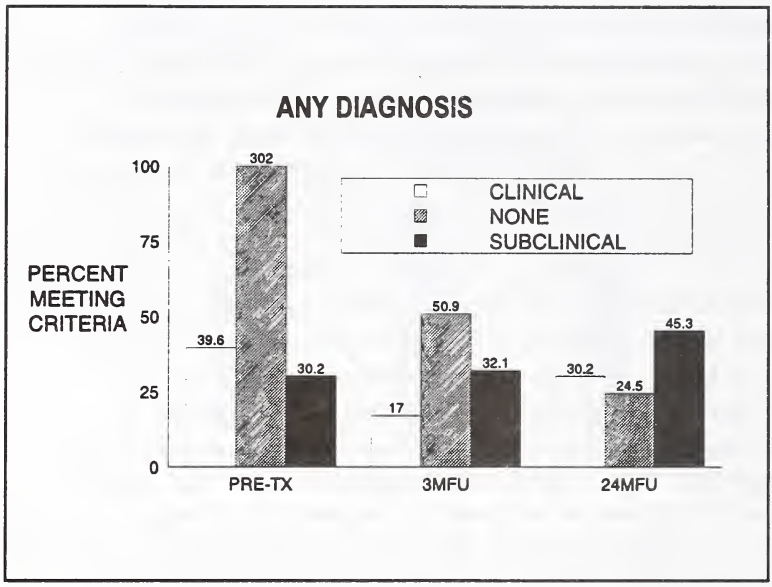

FIGURE 2. *Change in overall comorbidity rate following cognitive-behavioral treatment for PD.*

KEY: ANY DIAGNOSIS = presence of additional diagnosis irrespective of type; PRE-TX = pretreatment; 3MFU = 3-month followup; 24MFU = 24-month followup.

continued comorbidity met these criteria. Among the 36 patients who had not received any additional diagnoses at pretreatment, 6 (16.7 percent) were assigned a diagnosis other than PD at 24 months, but the remainder continued to be disorder free. Whereas 66.7 percent of the 30 patients who continued to have no comorbid diagnoses at 2 years met high end-state functioning criteria at this assessment point, only one (16.7 percent) of the six patients with a new additional diagnosis met these criteria.

There are two implications of this analysis for comorbidity between anxiety disorders and substance abuse. First, successful treatment of one disorder may only temporarily affect the course of the comorbid disorder when assessed longitudinally. Second, this comorbid disorder should be carefully attended to over the course of a long-term followup.

Furthermore, continued presence of a comorbid disorder bodes poorly for outcome of the original disorder. That is, treatment of the target disorder

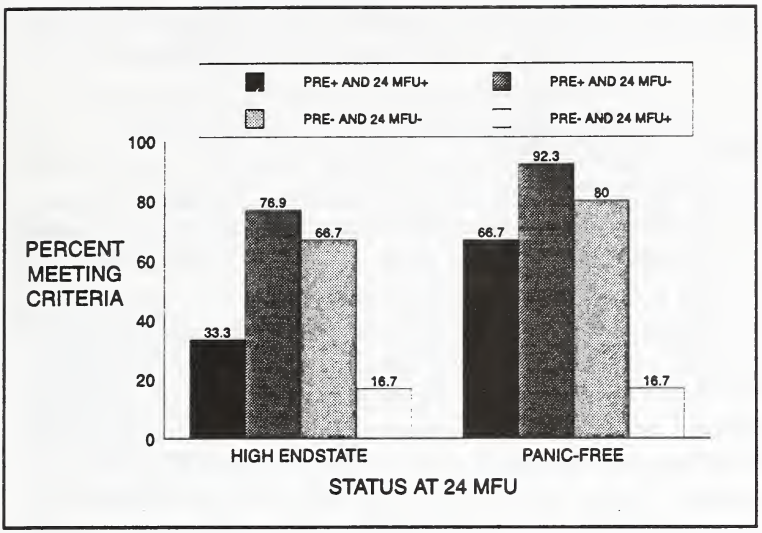

FIGURE 3. *Relation of longitudinal changes in comorbidity to treatment outcome at 24-month followup.*

KEY: PRE+ AND 24MFU+ = comorbidity present at both pretreatment and 24-month followup (24MFU); PRE+ AND 24MFU- = comorbidity present at pretreatment but not present at 24MFU; PRE- AND 24MFU- = comorbidity not present at either pretreatment or 24MFU; PRE- AND 24MFU+ = comorbidity not present at pretreatment but present at 24MFU.

is less successful in the presence of a persisting comorbid disorder. Thus, while existing pretreatment comorbidity does not seem to predict outcome in the target disorder, at least among the anxiety and mood disorders, additional comorbid diagnoses present at pretreatment are not likely to permanently remit, with the possible exception of reactive anxiety or depression. Moreover, the continued presence of an additional diagnosis at 24-month followup is associated with poorer outcome in the target disorder, in this case PD.

It is possible that these results are related to the functional relationship among diagnoses. That is, "reactive" depression and anxiety may permanently remit once the target disorder is treated, whereas more independent comorbid diagnoses may benefit only temporarily from treatment only to reemerge at a later point in time. Clearly, these

analyses have to be carried out with comorbid anxiety disorders and substance abuse and dependence while taking into consideration the temporal sequencing of these disorders in order to determine overall treatment strategies. The author found that, with the exception of generalized anxiety and depression, most anxiety disorders preceded the onset of alcohol abuse problems. On the other hand, the relationship between cocaine and PD in particular seems to reflect the opposite pattern of onset, with cocaine use triggering panic attacks and subsequently chronic PD after remission of cocaine abuse problems in a large proportion of those people suffering from PD. While treatment of PD seems successful whether triggered by drug use or not (Barlow 1988), few have attempted to treat anxiety disorders in the context of comorbid substance abuse. Some have argued that the presence of substance abuse would interfere with the results of many psychosocial treatments for anxiety disorders. This is because these treatments require the patient to experience anxiety in order to effectively learn new coping procedures and to make attributions of success to one's personal experiences. On the other hand, patients abusing alcohol might experience any anxiolytic effects as due to continued alcohol use and make those attributions.

While little data exist to support these arguments either way, some data do exist in another related area, specifically the use of benzodiazepines for anxiety disorders and the relationship of benzodiazepine use to successful psychosocial treatments. Specific problems that arise in this context involve the effects of benzodiazepines on psychosocial treatments for anxiety disorders and difficulties with discontinuing benzodiazepines.

BENZODIAZEPINE USE IN THE ANXIETY DISORDERS: RELATIONSHIP TO PSYCHOSOCIAL TREATMENTS

Benzodiazepines are commonly prescribed for anxiety disorders. Often these drugs are prescribed in low dosages by primary care physicians to control symptoms of anxiety before referring patients on to mental health professionals. For example, medication use in PD patients presenting for psychosocial treatment at two clinics known for psychosocial approaches are presented in table 1. As is evident, the overall percentage of patients on medication at time of presentation is approximately 60 percent, with fully 50 percent taking benzodiazepines. Interestingly, 40 percent of the total sample are taking one drug, the high potency benzodiazepine alprazolam. While these data were collected in the late 1980s, more recent experience at the author's clinic reflects few substantial changes. Of course, these

TABLE 1. *Medication use of PD patients presenting for psychological treatment.*

	Albany, NY[a]		Philadelphia, PA[b]		Overall	
	N	%	N	%	N	%
N not using medication	29	39	18	46	47	41
N using medication	46	61	21	54	67	59
Benzodiazepines	39	52	18	46	57	50
Alprazolam	33	44	12	31	45	39
Diazepam	4	5	2	5	6	5
Lorazepam	1	1	0	0	1	1
Chlordiazepoxide	1	1	3	8	4	4
Clonazepam	0	0	1	3	1	1
Tricyclic						
Imipramine	8	11	2	5	10	9
Other medication						
Propranolol	5	7	0	0	5	4
Buspar	0	0	1	3	1	1

KEY: a = Phobia and Anxiety Disorders Clinic, State University of New York at Albany. Based on two independent samples collected during 1986-1987 (Sanderson et al. 1990, 1989). b = Center for Cognitive Therapy, University of Pennsylvania. Data were collected during 1988-1989 (Sanderson and Beck 1989).

patients are still symptomatic or they would not be presenting for treatment. Thus, the use of benzodiaze-pines in this context can be analyzed as a predictive factor in assessing response to psychosocial treatment, as well as long-term outcome.

A few studies have examined this question. For example, Wardle and colleagues (1994), in one of the few prospective studies of its kind, examined the effects of very small doses (5 mg) of diazepam on the treatment of agoraphobia by in vivo exposure. The design of this experiment is presented in figure 4.

Specifically, those patients already utilizing drugs (users) or not (nonusers) discontinued drug use and then were introduced to either a placebo or 5 mg of diazepam in a double-blind fashion. They were then assessed once again prior to a course of in vivo exposure for their

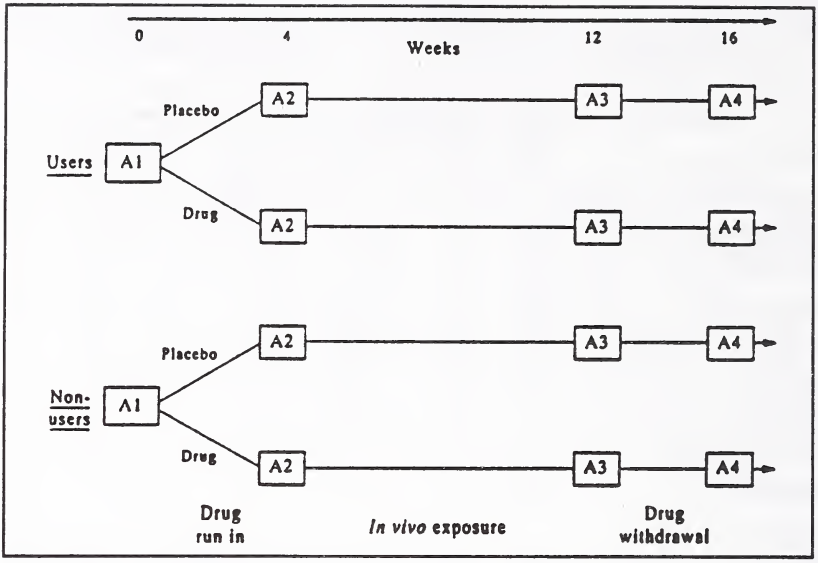

FIGURE 4. *Research design of study examining effects of low doses of benzodiazepines on in vivo exposure treatment of agoraphobia.*

SOURCE: Wardle et al. 1994.

agoraphobia before undergoing an additional assessment at 12 weeks after completion of in vivo exposure. After drug discontinuation they were assessed once again. While no effects were directly evident on measures of agoraphobia at any assessment point, global clinical ratings of improvement were slightly better after treatment for those patients on placebo as opposed to those on diazepam. This finding is potentially significant because of the small and certainly nontherapeutic dose of diazepam utilized in this experiment.

More recently Marks and colleagues (1993) examined the effects of more substantial therapeutic dosages of alprazolam as well as in vivo exposure either alone or in combination in the treatment of PD and agoraphobia. The major set of results demonstrated that patients did relatively well based on assessments immediately following treatment whether in vivo exposure was combined with alprazolam or not, with approximately 70 percent showing substantial clinical benefit. However, subsequent assessment after discontinuation from drug showed a substantially greater relapse in those patients taking alprazolam compared to those patients undergoing in vivo exposure without alprazolam. Thus, alprazolam

actually seemed to interfere with the therapeutic effects of in vivo exposure (see figure 5).

Finally, new data from the author's clinic suggest that at both the 3- and 24-month followup, those patients taking small and, in most cases, non-therapeutic doses of medication, mostly benzodiazepines, evidence a poorer outcome on measures of clinical severity than do those patients who are not using drugs even after controlling for initial levels of severity. Specifically, on overall measures of clinical severity from a semistructured interview, the Anxiety Disorders Interview Schedule-Revised (ADIS-R) (DiNardo and Barlow 1988), as well as ratings of fear

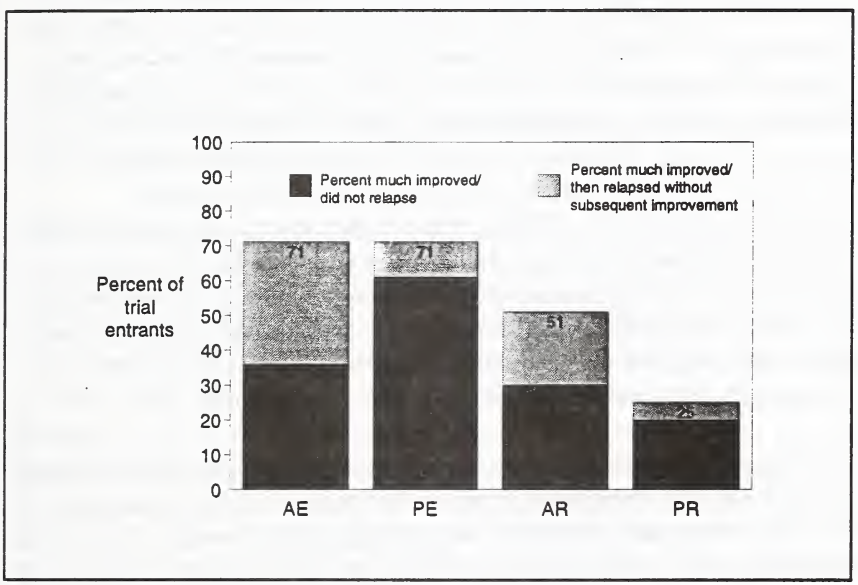

FIGURE 5. *Outcome of CGI at end of followup: percent of trial entrants who became much/very much improved on the assessor-rated CGI at any time and who remained so without major relapse to the end of the study at week 43.*

of panic from this same interview schedule, or scores on the Anxiety Sensitivity Index (Reiss et al. 1986) and subjective symptoms scale, reflecting impairment in functioning, those patients not taking drugs during treatment either did significantly better (from the ASI and ADIS-R–Fear of Panic Measure) or trended better (on the ADIS-R clinical severity and subjective symptoms scale measure) at the 24-month followup. Thus, it seems that benzodiazepine use may interfere with the

long-term effects of psychosocial treatment of anxiety disorders (Brown and Barlow 1995).

This is all the more striking since other classes of drugs such as the tricyclic antidepressants do not seem to interfere with psychosocial treatment. If anything, this class of drugs produces a synergistic effect when combined with psychosocial treatment (Barlow and Brown, in press).

Benzodiazepine Discontinuation

Concern over benzodiazepine prescribing practices has been growing in recent years (Roy-Byrne 1991; Tyrer 1988). These concerns focus mostly on the potential for abuse, dependence, cognitive and motor impairment, and difficulties associated with treatment discontinuation (Lader and Petursson 1983). Discontinuation is considered desirable for a number of reasons, including the reluctance of many individuals to undergo long-term treatment; concerns for safety over the long term, particularly in the elderly (Lader and Petursson 1983) or during pregnancy (Laegrid et al. 1987); and the need to reevaluate the necessity of continued antianxiety treatment in patients who have improved or recovered while on benzodiazepines (Rosenbaum 1990). Advantages of high potency benzodiazepines, on the other hand, include rapid onset of anxiolytic effects and more tolerable side effect profiles during acute treatment (Pollack and Rosenbaum 1988).

Attempts at discontinuation from benzodiazepines are associated with the onset of a specific withdrawal syndrome as well as very high relapse (Fyer et al. 1987; Nutt 1990; Noyes et al. 1991). For example, Noyes and colleagues (1988) found that nearly half of the patients treated with benzodiazepines for over 1 year experienced a withdrawal syndrome upon discontinuation of medication. For these and other reasons most patients are unable to complete benzodiazepine medication taper; this is true whether the taper is fast or slow (Pecknold et al. 1988) or whether the benzodiazepines have a long half-life or a short half-life (Rickels et al. 1990; Schweizer et al. 1990).

There is now some evidence that psychosocial treatments and benzodiazepines may be combined more effectively if applied sequentially. Some of this evidence comes from studies examining the effects of new brief psychosocial treatments to assist patients in discontinuing from benzodiazepines. A number of early case studies and clinical series suggest that a

combination of cognitive-behavioral strategies seems successful in assisting discontinuation (e.g., Tyrer et al. 1985; Higgit et al. 1987). More recently, Otto and colleagues have devised a treatment for purposes of benzodiazepine discontinuation (Otto et al. 1992, 1993). This approach was adapted from a successful treatment for PD (Barlow and Craske 1994). Spiegel and colleagues at Illinois have carried out a similarly successful effort (Spiegel et al. 1994).

In the Otto and colleagues (1993) study, 33 patients were randomly assigned to one of two taper conditions: a slow taper condition alone or a slow taper condition in conjunction with 10 weeks of group cognitive-behavioral treatment. All patients met criteria for PD with or without agoraphobia. Significantly, more patients receiving the cognitive-behavioral program (13 of 17; 76 percent) successfully discontinued benzodiazepine treatment compared to patients receiving the slow taper alone (4 of 16; 25 percent). Three-month followup evaluation indicated that 77 percent of patients in the cognitive-behavioral program remained benzodiazepine free.

Similarly, Spiegel and colleagues (1994) used an extremely gradual taper of as little as 0.125 mg every 7 days to attempt to discontinue PD patients who had been brought to a panic-free state with alprazolam. Ten patients received supportive therapy and 10 patients a cognitive-behavioral treatment (CBT) program modeled after Barlow and Craske (1994). With this slow taper, 90 percent of the CBT group and 80 percent of the comparison group successfully discontinued, but after 30 months only 40 percent of the comparison group remained off benzodiazepines, the others having resumed because of anxiety and panic symptoms. In contrast, all patients in the cognitive-behavioral group remained off medication. Results are presented in figure 6. These two studies have important implications for possible strategies for combining benzodiazepines and psychosocial treatments, as suggested below.

CONCLUSIONS

Results from all surveys indicate substantial comorbidity between anxiety disorders and substance abuse and dependence. Further analyses are needed to ascertain the functional relationship among these comorbid patterns and the long-term course of comorbidity as a function of treating one or the other disorder. For example, if substance abuse problems are essentially attempts to self-medicate an anxiety disorder, then successful

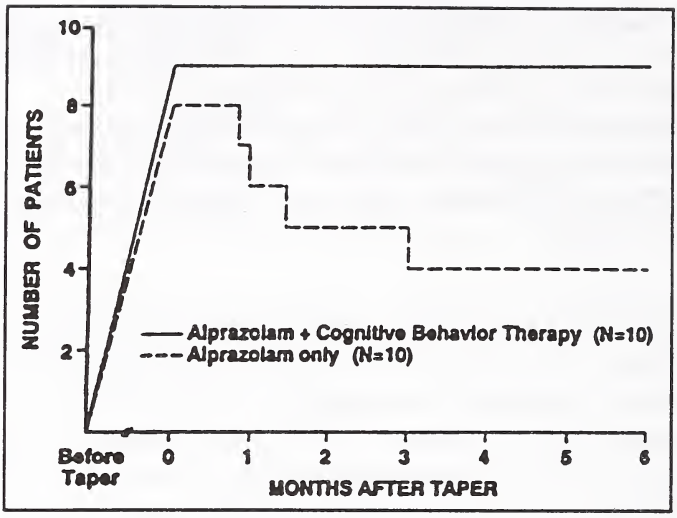

FIGURE 6. *Cumulative number of patients achieving and maintaining drug abstinence in groups receiving alprazolam only and alprazolam plus CBT.* [a]

KEY: a = Significant difference between survival distributions from before taper to after taper to 3 months after taper (Lee-Desu statistic = 4.197, df = 1, $p < 0.5$).

treatment of the anxiety disorder may also ameliorate the substance abuse disorder. On the other hand, if anxiety (or depression) is a reaction to substance abuse, then the initial target of treatment may have to be substance abuse-related issues.

Developing psychosocial approaches to benzodiazepine discontinuation may also have implications for the treatment of comorbid anxiety disorders and substance abuse. Specifically, the fact that patients treated psychosocially do less well over the long term if they are undergoing concurrent benzodiazepine administration may be due to one of several reasons. For example, benzodiazepine administration, insofar as it successfully reduces anxiety, may interfere with the emotional processing and development of coping procedures ongoing in cognitive-behavioral treatments in which confronting some anxiety is a necessary part of treatment. Alternatively, patients may attribute any anxiolytic effects to drugs that they happen to be taking, rather than to the development of

their own coping procedures and progress they have made in psychosocial treatment. Arguing against the latter interpretation is the fact that patients concurrently on other classes of medications, such as tricyclic antidepressants, seem to do as well or better after psychosocial treatment than patients not on tricyclic antidepressants. It may be that on a more fundamental neurobiological level, some classes of drugs are more compatible with psychosocial treatment than others.

In any case, it is also possible that a sequential administration of treatments beginning with high potency benzodiazepines with their quick onset, followed by cognitive-behavioral approaches to not only assist in discontinuing benzodiazepines but also to produce long-term effects, will be a useful treatment strategy (Barlow and Brown, in press; Spiegel et al. 1994). This has yet to be demonstrated.

Finally, for those individuals who began abusing substances in attempts to self-medicate anxiety, it may be that, contrary to current clinical wisdom, administration of psychosocial treatments targeting anxiety will at the same time evidence beneficial effects on substance use. This approach might provide a more reliable long-term strategy not only to assist withdrawal from substances but also to promote long-term maintenance of treatment gains and prevent relapse. Studies evaluating this possibility lie ahead.

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Cigarette Smoking and Its Comorbidity

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Comorbidity is the existence of two conditions in the same individual at a greater frequency than would be expected by chance alone. The existence of such associations says nothing about the underlying cause of the comorbidity. Cigarette smoking in the United States has long been associated with an increased level of psychiatric symptomatology, but until recently this was not thought of in terms of specific diagnostic entities. Cigarette smokers were simply thought more likely to be "nervous" people than nonsmokers (Glassman 1993). However, it is important to realize that the appearance of comorbidity can be strongly influenced by social factors. If everybody smoked, there could be no association between smoking and any psychiatric condition.

In 1985, while testing a new drug for smoking cessation, Glassman and colleagues (1988) noted what they felt was an astounding lifetime rate of major depression among smokers coming to the clinic. Forty-two of 71 smokers (60 percent) had a history of major depression, while the best available data suggest lifetime rates for the general community of around 18 percent (Kessler et al. 1994). This threefold increase in the observed rate of major depression was even more dramatic than it might first appear because smokers coming to the clinic were screened to exclude individuals who were presently ill. Whereas community epidemiological data represent both individuals presently ill and those with only a past history of major depression, the clinic sample consisted only of smokers with a past history of depression. In retrospect, it is likely that the extraordinarily high rate of prior major depression observed by the researchers was an artifact of the particular academic population that they had happened to study.

The vast majority of the 71 smokers who participated in the study were either postdoctoral students or faculty at Columbia University, and most came from the medical school campus. This finding was undoubtedly related to the exceptionally high rate of major depression observed. Medical school faculty and their graduate students face considerably more social pressure to give up smoking than the general population. It would seem reasonable to assume that in groups where awareness of the

health risks increases and social pressure to stop smoking grows, those who can quit easily do so and those who remain smokers are individuals more vulnerable to nicotine.

Hughes and associates (1986) had earlier shown that patients coming to a medical center for treatment of a variety of psychiatric conditions, including depression, were more likely to be smokers than the general population. That seemed intuitively reasonable. However, once the strength of the association with a specific history of depression became apparent, it seemed worthwhile to determine whether a history of major depression influenced smoking cessation—and it did. Again, that patients presently depressed have more difficulty quitting than individuals not depressed seems obvious; however, the finding that a history of depression would still be associated with cessation failure, even when an individual had been euthymic for a considerable period of time, was not so obvious and required replication.

The first two replications both came from previously existing data sets. The St. Louis node of the Epidemiological Catchment Area (ECA) study contained both psychiatric diagnostic information and smoking history on over 3,200 randomly selected community residents (Glassman et al. 1990). Among those individuals with either no psychiatric illness or any psychiatric illness except major depression, 47 percent of the women and 68 percent of the men had at some time in their lives been regular smokers. By comparison, among those individuals with a history of major depression, 65 percent of the women and 80 percent of the men had been regular smokers. The increases among both men and women are highly significant, but the increased rate among the depressed women is particularly striking. The data on cessation also very much paralleled the data for the original small clinical sample. Thirty-one percent of those smokers with no history of any psychiatric history were able to stop smoking for more than 1 year, and 28 percent of those individuals with either no psychiatric history or no psychiatric history except major depression were able to quit. Among those with a lifetime history of major depression, less than 14 percent of smokers were able to stop and remain abstinent.

Similarly, data on 3,023 individuals from the National Health and Nutrition Examination Survey (N-HANES) also demonstrated an increased rate of smoking and a decreased rate of quitting associated with increasing levels of depression (Anda et al. 1990). The major difference between the ECA and the N-HANES data sets is that the ECA instruments classified

individuals by diagnosis, while N-HANES obtained only symptomatic measures of depression.

A subsequent community survey also produced by the Centers for Disease Control and Prevention was the Hispanic NHANES, which studied 3,337 individuals of Mexican origin and obtained both symptomatic and diagnostic measures of depression on this sample (R.F. Anda, personal communication, January 11, 1995). It is important to understand that this is an epidemiology survey that records lifetime rates of illness, and lifetime major depression involves both cases that are presently ill and cases of past illness. Presently ill cases will always show symptoms of depression as well as meeting diagnostic criteria. However, cases of past history may or may not presently have symptoms of depression. Both those individuals with symptoms but no diagnosis and those with a diagnosis but no symptoms showed higher rates of smoking than individuals with neither condition. However, individuals with both a diagnosis and symptoms of major depression showed the highest rates of smoking. Thus, there is now evidence that symptoms, as well as a diagnosis of major depression, are associated with cigarette smoking.

These data are somewhat more complex than is readily apparent. It might seem that symptoms of depression and major depression alone are approximately equal in their likelihood of being associated with cigarette smoking. However, it is probable that the cases of major depression in the major depression-only group will be less severe and less likely to be recurrent than those cases in the group with both major depression and present symptoms of depression. Recurrent major depression has regularly been shown to have higher levels of interepisode depressive symptomatology (Keller et al. 1983; Dalack et al. 1995) than single episode cases. Thus, it seems probable that the major depression-only group will contain a greater proportion of single episode cases of major depression. Cases of single episodes of major depression have already been shown in both clinical (Glassman et al. 1993) and epidemiological (Covey et al. 1994) research to be less strongly associated than recurrent major depression with cigarette smoking. As a result, it would seem likely that both individuals with symptoms of depression and individuals with a single episode of major depression are more likely to be smokers than individuals with no history of either condition. In addition, the association between smoking and depression will be strongest among those individuals with either recurrent major depression or major depression and high levels of chronic depressive symptoms. There is also evidence that a similar step function exists with the intensity of smoking. At least

among women, Kendler and associates (1993) have replicated the finding that heavier smoking is associated with an increasing likelihood of a lifetime history of major depression, and Breslau and associates (1993) have shown that this same association is greater in dependent than in nondependent smokers.

One of the issues not dealt with adequately in any of these three large data sets is the role of other psychiatric diagnoses. Breslau has examined 1,200 young adults (Breslau et al. 1991) and Kendler has data on 1,566 female twins (Kendler et al. 1993). Breslau replicates the previously observed associations between major depression and both smoking and smoking cessation. Kendler does not examine cessation, but does find a strong association between smoking and a lifetime diagnosis of major depression. However, these studies provide information that earlier data sets were not designed to address. As a major example, both Breslau and Kendler demonstrated that the relationship between major depression and smoking persists even after controlling for both alcohol and anxiety disorders. Both also showed that the association was most robust among heavier or more dependent smokers.

Beyond these observations, Kendler's study is uniquely valuable because it was done in twins. Community epidemiological surveys can identify an association; however, they allow no conclusion about the source or cause of an association. Cederloff and colleagues (1977) have shown that community surveys in twins allow inferences to be drawn about the source of an association. Ordinarily, twin pairs will be concordant for most behavioral characteristics. If there is an association between two characteristics, such as depression and smoking in the general population of twins, then the discordant dizygotic and monozygotic pairs, even though they are a minority of the pairs, are informative about the etiology of that association. If smoking damages the brain, for example, then the behavior (smoking) would be associated with depression. The increase in the odds ratio would be the same in the general population (of twins) and in both discordant monozygotic and dizygotic twins, and smoking would be associated with depression independent of zygocity. If, on the other hand, the association was based on familial or environmental factors, an association seen in the general population of twin pairs would not be found in either the discordant monozygotic or dizygotic twin pairs because they share those factors equally. If, however, the association was the result of genes, then no association would be seen in the monozygotic discordant twins because of their identical genes, but an intermediate association (a value between monozygotic discordant and the general

population in twins) could be expected among the dizygotic discordant pairs because they share only about half of their genes. The pattern seen with common or shared genes as the source of the association is precisely what Kendler observed (Kendler et al. 1993).

Breslau, using community epidemiological data obtained at two different points in time, made observations that are entirely consistent with Kendler's results (Breslau et al. 1993). Studying 1,200 young adults, examined initially and then again 18 months later, Breslau found that smokers who had no history of depression at the first examination were twice as likely to develop depression as were nonsmokers with no history of depression. Similarly, those individuals with a lifetime history of major depression who did not smoke at the first examination were twice as likely to become smokers as those individuals who did not smoke but who had no evidence of major depression at the first examination. This finding is exactly what the Kendler twin data would predict.

In addition to the available epidemiological data, the association between depression and both smoking and smoking cessation has also been replicated in several smoking cessation clinics (Glassman et al. 1988, 1993; Hall et al. 1992; Kinnunen et al. 1994). Thus, in the relatively few years since these associations with depression were first observed, they have been extensively replicated, and there is even fairly strong evidence that the association between smoking and lifetime major depression, at least in women, is based on common genes. One aspect of these data that is not clear is the relationship to gender.

The association between major depression and ever smoking has been seen in both men and women, but it appears to be stronger in women than men. Similarly, the association between major depression and smoking cessation has been demonstrated in both men and women, but when the relationship is not apparent, it most often has not been found in males. The same preponderance of positive observations among females exists in studies that focused on symptoms of depression rather than on a diagnosis of major depression (Frederick et al. 1988; Perez-Stable et al. 1990; Anda et al. 1990). The question of whether nicotine is a potentially more addicting substance among either women in general or among women at risk for depression may not be an answerable question. It could be that the genes common to smoking and depression exert an equal influence in males and females and that the apparent strength of the relationship in women is merely an artifact of the increased frequency of depression in women. However, social factors clearly influence the

likelihood of smoking and, until recently, men were much more likely to smoke because there was a higher social barrier to women smoking. The high rate of smoking, combined with the lower rate of depression in men, sets mathematical limits on the odds ratio for smoking in depression that are significantly less than for women. If the relative risk for smoking among depressed women were approximately 2, and 65 percent of men had a lifetime history of smoking, then more than 100 percent of the depressed men would smoke if the relative risk were also 2 among the men. Obviously, that is impossible. Even now that the rate of initiating smoking is essentially the same among men and women, it is not necessarily true that the relative proportion of genetic and social factors involved in initiating the behavior are the same in males as females. As a result, the association between smoking and major depression and the origin of that association need to be examined separately in men and women. What appears to be true is that the existence of major depression, and probably recurrent disease in particular, increases the likelihood of smoking behavior and decreases the odds of stopping that behavior. Because social factors can play a major role in these same behaviors, it will be easier to observe the effect of depression when social pressures tend to inhibit the initiation and encourage the cessation of smoking—a pattern that is probably true for most drugs of abuse.

In addition to the evidence linking smoking and smoking cessation failure to major depression, there is now considerable evidence that, in individuals with a history of major depression, successful smoking cessation can provoke the onset of severe depression. Most of the evidence to support this consists of case reports (Flanagan and Maany 1982; Glassman et al. 1993; Stage et al., in press). However, data have recently been published from a study in which 300 smokers, before attempting cessation, were given a psychiatric diagnostic examination (Glassman et al. 1993). One smoker among 153 individuals with no baseline evidence of psychiatric illness became so depressed during withdrawal from cigarettes that the therapist felt it necessary to recommend that the person return to smoking. In comparison, 6 smokers among 113 with a history of major depression became so depressed as to require the therapist to recommend resumption of smoking (odds ratio 8:5). These observations, among other things, constitute further evidence for a relationship between cigarette smoking and major depression.

Certainly depression and major depression are not the only psychiatric conditions that are comorbid with cigarette smoking. They are discussed here in detail because the detail is available. Chronic schizophrenic

patients smoke at a rate that approaches 90 percent (Lohr and Flynn 1992; Goff et al. 1992), but, beyond the remarkable frequency of the behavior, little else is known about the relationship. No information is available on the relation to the phase of the illness, the type of symptomatology, or the severity of the addiction. In fact, nothing is known about any details of the relationship between smoking cessation and schizophrenia. The other striking comorbidity is between cigarette smoking and other drug addictions, but again, almost nothing is known about these relationships except that they exist. It is rare to see an alcoholic who does not also smoke, yet almost nothing is known about the reasons behind this relationship. Some experts have speculated that because nicotine is a stimulant drug, it makes functioning easier or allows intake of higher levels of a basically depressant drug like alcohol. If there is some more fundamental basis, like the shared genes seen with smoking and depression, it is, again, unknown. It is important to know if smoking cessation is associated with increased craving for alcohol and/or alcoholic relapse in a way similar to its provoking depression in smokers with a history of depression, but, again, data are not available. The same questions arise with the other drugs of abuse, and the same lack of answers exists.

The association of specific psychiatric illness with various drugs of abuse is striking. In many ways it is easiest to examine nicotine, but the association is in no way less likely to occur or less important with any addicting drug. The basis of these associations may not be the same for different psychiatric conditions or for different drugs of abuse. However, careful study of such associations is likely to prove profoundly important to the basic understanding of either condition.

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Treatment of Depression in Drug-Dependent Patients: Effects on Mood and Drug Use

Edward V. Nunes and Frederic M. Quitkin

INTRODUCTION

Symptoms of depression and anxiety are common in patients with substance use disorders (Meyer 1986; Schuckit 1986). In the general population, mood and anxiety disorders convey increased risk for substance use disorders (Regier et al. 1990). Further, mood-disordered substance abusers have poor prognoses (Rounsaville et al. 1982*b*, 1986*b*, 1987; Weissman et al. 1976; Kosten et al. 1986; LaPorte et al. 1981; Loosen et al. 1990; Carroll et al. 1993). Thus, evaluation and appropriate management of affective disorders should be a useful treatment adjunct with the potential of improving outcome of substance abuse. Nevertheless, controversy continues to surround this clinical problem, and approaches vary widely among clinicians.

Further, the problem of the depressed substance abuser raises important theoretical questions about the etiology and pathogenesis of substance abuse disorders. Mood syndromes observed in substance-dependent patients often resolve soon after abstinence or the initiation of specific treatment such as methadone (Weddington et al. 1990; Rounsaville et al. 1986*a*; Schuckit 1986; Willis and Osbourne 1978; DeLeon et al. 1973), suggesting a "substance-induced" (American Psychiatric Association 1994) syndrome (i.e., toxicity or withdrawal) or transient adjustment reactions. However, in 10 percent or more of these patients in various clinical samples, depression persists (Nakamura et al. 1983; Johnson and Perry 1986; Rounsaville et al. 1986*a*; Croughan et al. 1981). These persons may have a mood disorder that is independent of substance abuse. Because both substance abuse and mood disorders are common in the general population, it can be expected that some individuals will have both disorders by chance alone.

Another possibility is that a subgroup has mood disorders that contribute to the etiology of substance abuse. In fact, a self-medication hypothesis has been advanced (Khantzian 1985; Quitkin et al. 1972) suggesting that

some individuals use drugs because they provide temporary relief from symptoms of depression or anxiety. Depression or anxiety may be the sole etiology or one of several causal factors, including other genetic and environmental vulnerabilities, in substance abuse. Also, depression or anxiety may alter the course of substance abuse. For example, depression is a frequent internal cue triggering drug craving (Marlatt and Gordon 1985; Daley and Marlatt 1992). Thus, an initially independent depressive disorder, through classical conditioning (Childress et al. 1994), may become linked to relapse and perpetuate substance abuse.

The evidence that the self-medication hypothesis plays a contributory role in some substance abuse stems mainly from clinical observations (Khantzian 1985; Marlatt and Gordon 1985) and epidemiologic data (Regier et al. 1990). However, the strongest test of the hypothesis would be one that directly addresses its clinical utility, namely, whether treatment of depression or anxiety alters the course and outcome of substance abuse. Specifically, if depression contributes to the etiology of substance abuse, then antidepressant treatment should improve substance abuse outcome. Relatively few studies of this type have been undertaken, and most have methodologic problems. This chapter reviews this literature as well as the authors' recent studies, drawing tentative conclusions and developing suggestions for future research.

The present approach to evaluating the literature is summarized in table 1 (Nunes et al., in press). Studies evaluated are those in which patients with substance use disorders who also display evidence of depression receive antidepressant medication treatment. If there is no medication-placebo difference in both mood and substance use outcome (right column, table 1), and particularly if the placebo-mood response is high, a transient substance-induced mood syndrome or adjustment reaction is suggested. If mood improves on medication compared to placebo, but substance use does not (middle column, table 1), it suggests a true mood disorder that is independent of substance abuse. Finally, if both mood and substance use improve on medication (left column, table 1), it suggests that the depression contributes to the etiology of substance abuse, as in self-medication.

Antidepressant Treatment in Alcoholism

In the 1960's and 1970's, nine placebo-controlled studies of antidepressant medications (mainly tricyclics) (TCAs) in alcoholic

TABLE 1. *Predicted outcome of antidepressant treatment across mood disorder/substance abuse relationships.*

	Depression contributes to substance abuse: "self-medication"	Depression and substance abuse are independent	Depression is substance-induced
Mood improves (vs. placebo)	Yes	Yes	No (high placebo resonse)
Drug use improves (vs. placebo)	Yes	No	No

SOURCE: Adapted from Nunes et al. 1994.

patients were reported. These studies have been reviewed extensively by Ciraulo and Jaffe (1981) and by Liskow and Goodwin (1987). No study demonstrated superiority of TCAs except for some short-lived effects, probably attributable to amelioration of withdrawal symptoms. However, both research pairs concluded that the studies were seriously flawed and that further study of antidepressant medication treatment of depressed alcoholics was needed. Both the doses of TCAs and the trial lengths (mostly 3 weeks or less) were inadequate. Outcome measures were narrowly focused on either depression or drinking behavior, but not both. Methods of diagnosing affective disorder were either unspecified or based on cross-sectional scales, which are not adequate measures of primary affective disease in the setting of alcoholism (Keeler et al. 1979).

One promising pilot study did demonstrate successful open treatment with imipramine of a small series of alcohol and sedative abusers with panic disorder (Quitkin et al. 1972). This study had the advantage of a carefully diagnosed, homogeneous sample, but required replication in larger controlled trials.

In a first replication attempt, Nunes and colleagues (1993) conducted an open-label trial of imipramine followed by double-blind, placebo-controlled discontinuation for responders. Subjects were outpatients who currently met criteria for *Diagnostic and Statistical Manual of Mental*

Disorders, 3d ed. revised (DSM-III-R) (American Psychiatric Association 1987) alcohol abuse or dependence and also had DSM-III-R major depression or dysthymia. Experienced research psychiatrists interviewed and diagnosed the patients. Depressive syndromes were either chronologically primary, antedating the onset of alcohol abuse on a lifetime basis, had persisted during past abstinent periods, or were chronic.

Eighty-five patients met inclusion criteria and entered the trial, and 60 completed the minimum adequate trial of 6 weeks of imipramine. The mean dose of imipramine was 263±77 mg/day and the mean blood level was 368±264 nanograms per milliliter (ng/mL). In addition to weekly visits with a treating psychiatrist, each patient received one weekly session of alcoholism counseling, and all patients were encouraged to attend Alcoholics Anonymous. Of the 60 completers, 27 (45 percent) were rated as "responders" to open imipramine after the initial 12 weeks with a substantial improvement in both mood Clinical Global Impression (CGI) change score of 2, "much improved," or 1, "very much improved," and drinking behavior. A rating of substantial improvement in drinking required either abstinence (18 cases, 30 percent) or a substantial reduction in quantity consumed and an absence of functional impairment. Another three patients responded after increases in imipramine dosage, and five more responded after brief courses of disulfiram, so that a total of 35 (58 percent) were ultimately called responders.

Twenty-three of the responders entered and completed the 6-month, double-blind discontinuation phase in which they were randomized either to remain on imipramine or taper off imipramine onto placebo. The principal endpoint was relapse during the 6-month followup period, defined as loss of either mood response or drinking response or both. The relapse rate was lower on imipramine (31 percent, 4/13) than on placebo (70 percent, 7/10), a difference that approached statistical significance (Fisher's exact $p = 0.09$, two-tailed). Most relapses involved near-simultaneous return of both depression and drinking.

This study differed from previous research by providing a medication trial of adequate dosage and duration, and by selecting depression via syndromal criteria rather than cross-sectional symptoms. The results suggest that antidepressant medication treatment is useful in depressed outpatient alcoholics, both in treating depression and in inducing remission of drinking and preventing relapse. The findings provide

preliminarily support for the hypothesis that depression plays some role in the etiology of drinking in a selected subgroup.

Replication is clearly needed in larger controlled trials, along with further work on developing criteria for selecting medication-responsive depressed alcoholics. The majority of patients selected for this trial had depression that was chronologically primary, because the investigators felt that this history would characterize self-medicators. Interestingly, Mason and Kocsis (1991) recently completed a methologically sound, placebo-controlled trial of desipramine in alcoholics who all had depression that was chronologically secondary, but had persisted during inpatient detoxification. Their results also suggested that desipramine was useful in treating both depression and drinking (Mason and Kocsis 1991). This suggests that the primary-secondary distinction may be of limited utility as a selection criterion, since both primary and secondary depressions appear to respond to medication. Persistence of depression after inpatient detoxification may be more useful, although in practice it is not always possible to arrange hospitalization.

LITHIUM TREATMENT OF ALCOHOLISM

Lithium has actually been extensively studied as a treatment for alcoholism. The older literature contains four double-blind, placebo-controlled studies (Fawcett et al. 1984, 1987; Pond et al. 1981; Merry et al. 1976; Kline et al. 1974) in which patients were not selected for depression, but outcome was compared in depressed and nondepressed subgroups. A principal hypothesis of the studies was that lithium would have a direct effect on drinking behavior independent of its mood-stabilizing effects. Depression was assessed with cross-sectional scales rather than by clinical history and syndromal diagnosis. In three of the studies (Fawcett et al. 1987; Merry et al. 1976; Kline et al. 1974), lithium-treated patients showed a significant reduction in alcohol consumption compared to controls. In the fourth study this effect held only for the depressed subgroup (Merry et al. 1976). However, none of the studies detected a significant reduction of depression symptoms in the lithium-treated groups compared to placebo groups. Depression scores tended to be reduced at followup in all subjects, suggesting a high placebo response rate. On balance, these early findings suggested that lithium might have a salutary effect on alcoholism that might be unrelated to its mood-altering effect. Another possibility is that lithium might modulate alcohol intake via serotonergic mechanisms, reminiscent of

preclinical studies suggesting that serotonin uptake inhibitors may reduce self-administration of alcohol (Gorelick 1989; Naranjo et al. 1990) and cocaine (Carroll et al. 1990; Kleven and Woolverton 1993). The suggestion is instructive because it highlights the possibility that an antidepressant medication might directly influence the pathophysiology of addiction quite apart from any effects on mood.

Subsequently, a large and well-designed multicenter trial failed to detect any effect of lithium on drinking behavior, even in the subsample with syndromal major depression (Dorus et al. 1989). This failure to replicate is consistent with several possibilities, including that of a very modest efficacy of lithium. However, the findings are inconclusive on the notion of a medication-responsive depressed subgroup. The data indicate that a lithium-responsive depressed subgroup seems unlikely, but lithium is at best a modestly effective antidepressant.

Antidepressant Treatment in Cocaine Abuse

In an approach reminiscent of studies on lithium in alcoholism, a number of placebo-controlled trials of desipramine (Gawin et al. 1989; Giannini and Billett 1987; Weddington et al. 1991; Arndt et al. 1992; Kosten et al. 1992; Carroll et al. 1994) have been conducted to test whether desipramine has a direct effect on cocaine use behavior, independent of its antidepressant effects. This hypothesis stems in part from preclinical studies showing that tricyclic antidepressants reverse stimulant-induced changes in intracranial self-stimulation (Markou et al. 1992). Depression was not an inclusion criterion for these studies.

In the first large trial in this series, Gawin and colleagues (1989) showed a robust, favorable effect of desipramine on cocaine use and craving. The effect was not diminished when the small subgroup with major depression was removed from the analysis, suggesting that it was indeed independent of any antidepressant effects. Large placebo-controlled trials have subsequently failed to replicate the robust effect, although several suggested that a desipramine effect may occur early in treatment (Kosten et al. 1992, Carroll et al. 1994) or in the mildly ill subgroup (Carroll et al. 1994). Of interest to this review, a secondary analysis of one of the studies (Ziedonis and Kosten 1991) showed a favorable effect of desipramine on cocaine use in the subsample with depression at baseline. Also several studies demonstrated a desipramine effect on mood (Giannini and Billett 1987) or psychological symptoms (Arndt et al. 1992). Similarly, preliminary analysis of a study by the authors of

imipramine for cocaine abuse suggests that tricyclic antidepressants may reduce cocaine use in the subsample with depression (Nunes et al. 1995).

Fluoxetine also showed some promise for treatment of cocaine abuse in initial open (Batki et al. 1991) and placebo-controlled trials (Batki et al. 1993), although subsequent placebo-controlled trials (Covi et al. 1995, Grabowsky et al. 1995) have failed to replicate these findings. Once again, depression was not an inclusion criterion. To date, no study of either desipramine or fluoxetine has focused exclusively on depressed cocaine abusers.

Antidepressant Treatment in Opiate Addiction

During the 1970's and early 1980's, six randomized, double-blind, placebo-controlled trials of tricyclic antidepressants in methadone-maintained or detoxifying opiate addicts were reported (Kleber et al. 1993; Woody et al. 1982, 1975; Goldstein et al. 1992; Titievsky et al. 1982; Batki et al. 1987). These studies, summarized in table 2, were stronger methodologically than the older literature on TCAs in alcoholism, and in contrast to the studies on antidepressants for cocaine abuse, they all selected subjects with evidence of current depression. All but one (Titievsky et al. 1982) measured both mood and drug use outcomes. Sample sizes were mainly small ($N < 50$). Trial lengths were usually 4 weeks, which is adequate, although minimally so (Quitkin et al. 1984). Doses of tricyclics were low (Quitkin 1985). However, methadone slows the metabolism of TCAs (Kosten et al. 1990), so that adequate blood levels may actually have been achieved, even though blood level monitoring was not employed.

As shown in table 2, four of five studies employing doxepin report superiority to placebo on measures of depression (Goldstein et al. 1982; Woody et al. 1975; Titievsky et al. 1982; Batki et al. 1987). Three found medication superior to placebo on at least a few self-report drug abuse outcome measures (Woody et al. 1982, 1975; Batki et al. 1987). However, another three either lacked drug abuse outcome measures (Titievsky et al. 1982) or detected no medication versus placebo differences on drug abuse measures (Kleber et al. 1983; Goldstein et al. 1982). No studies found doxepin effects on urine toxicology. Thus, the evidence for a doxepin effect on drug abuse is equivocal.

TABLE 2. *Double-blind, placebo-controlled trials of tricyclic antidepressants in methadone patients.*

Author, year	Sample size	Medication, dose range, duration	Depression inclusion criterion	Depression outcome drug > placebo	Drug use outcome drug > placebo
Woody et al. 1975	35	doxepin 150 mg/day, 4 weeks	clinical psychiatric interview	+	+/-
Titievsky et al. 1982	46	doxepin 200 mg/day, 4 weeks	Ham-D > 18	+	not reported
Woody et al. 1982	30	doxepin vs desipramine 4 weeks	unspecified	+/- P*	+/-
Goldstein et al. 1982	44	doxepin 100 mg/day, 12 months	unspecified	+/- P*	-
Kleber et al. 1983	46	imipramine 150-225 mg/day, 8 weeks	clinical interview (DSM-II) Raskin > 7	- P*	-
Batki et al. 1987	81	doxepin 12 weeks	DSM-III major depression	+/-	+/-

KEY: * P = High placebo response rate observed in depression outcome measures.

SOURCE: Adapted from Nunes et al. 1994.

In a three-group design, Woody and associates (1982) found trends suggesting that desipramine was no better than placebo and inferior to doxepin, although the sample size (N = 10 per cell) was too small for a conclusive analysis. Another study found that imipramine had no effect on either depression or drug abuse (Kleber et al. 1983). Because imipramine and desipramine are relatively nonsedating TCAs, the suggestion is that doxepin may work in this population through nonspecific sedative effects (Kleber et al. 1983; Woody et al. 1982).

In summary, several of these studies demonstrated clear-cut antidepressant effects of TCAs in opiate addicts, but none demonstrated clear effects on drug abuse outcome. These findings suggest that depression can be identified and treated in methadone maintained opiate addicts, but is, at least in many cases, an independent disorder that does not contribute to the etiology of addiction.

It is also possible that methodologic shortcomings, including inadequate doses and trial lengths, contributed to a failure to demonstrate decreased drug use. Further, the placebo groups improved substantially in three of the trials (Kleber et al. 1983; Woody et al. 1982; Goldstein et al. 1982). A high placebo response rate makes detection of medication effects difficult, suggesting that the samples were heterogeneous and primarily evidenced transient dysphorias that resolved spontaneously. All studies studied depressed patients using cross-sectional symptom scales rather than clinical history and syndromal diagnosis. As noted, depression in opiate addicts is often transient (Rounsaville 1986*a*; DeLeon et al. 1973), which suggests that antidepressant treatment of homogeneous samples with primary or chronic affective disease would yield more robust effects on mood and drug use.

With the benefit of hindsight on earlier design shortcomings, the authors and colleagues have sought to test the effectiveness of a standard antidepressant, imipramine, for the treatment of depression and drug abuse in methadone patients. Designs included minimum adequate trial lengths of at least 6 weeks, dosages of 150 to 300 mg/day, and selection of depressed subjects through diagnostic interviews by experienced clinicians who applied stringent criteria for current and lifetime DSM-III-R depressive syndromes.

Pilot Trial

The initial study was an open-label pilot trial of imipramine in a consecutive series of depressed methadone patients (Nunes et al. 1991) at a university-affiliated, community-based methadone clinic (site 1). Depression was diagnosed only if the patient met criteria for current DSM-III-R major depression or dysthymia that was either primary, had persisted during a past abstinence, or was at least of 6 months' duration in the current episode. Diagnosis was made through clinical history by experienced research psychiatrists. Twenty-four patients (10 men, 14 women) entered and 17 (7 men, 10 women) completed a minimum adequate trial of at least 6 weeks of imipramine at doses ranging from 100 to 300 mg/day (median: 250 mg/day). Of the 17 completers, 16 were using illicit drugs at baseline, 9 of 17 intravenously, and one was abstinent but experiencing strong drug cravings. Baseline Hamilton Depression (HAM-D) Scale scores ranged from moderate to severe, with a mean of 17 ± 4. Nine patients (53 percent) were judged "responders," with marked reductions in both depression (mean posttreatment HAM-D 2 ± 1) and illicit drug use. All patients gave weekly urines. For each patient, the percentage of urines positive for any drug, using a mirror image historical control (i.e., 6 months prior to initiation of the imipramine trial), was compared to the proportion of positive urines in a followup period of up to 11 months during which patients were maintained on imipramine. Among responders the percentage of positive urines was 54 ± 26 at pretreatment, which dropped to 15 ± 17 during treatment.

The nine responders in the open trial were offered continuing psychiatric treatment at the methadone clinic. Chart review of their treatment course over 4 years of followup (Nunes et al., in press) showed that depression remained improved during imipramine treatment, but relapses often occurred during attempts to taper the medication. This finding suggests that imipramine exerted a continuing antidepressant effect, although drug use recurred intermittently for several patients despite ongoing imipramine treatment, and suggests a less robust effect of the antidepressant on drug abuse.

Double-Blind, Placebo-Controlled Trial

Because the uncontrolled trial suggested that antidepressant treatment had a substantial effect on both mood and drug use in carefully selected, depressed methadone patients, the authors conducted a larger, placebo-

controlled imipramine trial. Following is a preliminary analysis of outcome for the first 80 patients to complete the study.

Sample and Methods. The design was a prospective, parallel groups, randomized, placebo-controlled trial of imipramine in methadone patients with current depression who met lifetime historical criteria similar to those described for the open-label trial. Because of the high placebo response rates experienced in other trials, patients were required to have been in methadone treatment for at least 1 month preceding study onset in order to be included, which was a further effort to exclude transient mood syndromes. The trial was conducted at the same site as the open-label trial, as well as at a second university-affiliated, community-based methadone clinic.

Global Outcome. The primary outcome measure, defined a priori, was a dichotomous response criterion requiring both a rating of at least much improved on the Clinician's Global Impression scale score for depression and at least a 75 percent reduction in self-reported drug use or of abstinence. Twenty-four of 40 (60 percent) of completers on imipramine were responders, compared to 3 of 40 (8 percent) on placebo ($\chi^2 = 24.3$, 1 df, $p < 0.0001$). The imipramine-placebo difference was equally robust among men, women, whites, and minorities and was similarly unaffected by clinic site or type of depression (major versus nonmajor depression, or primary versus nonprimary depression). Thus, imipramine continued to be effective, and low placebo response rate suggests that the diagnostic approach succeeded in excluded patients with transient, self-limited mood disturbances.

Continuous Outcome Measures. Preliminary analysis of continuous outcome measures reveals a mixed picture. There is a robust difference between imipramine (7.3 ± 6.6) and placebo (13.5 ± 6.3) on the post-treatment HAM-D Scale total score (effect size = 0.96) ($F = 23.3$, 75 df, $p < 0.001$). For self-reported days of use per week of each patient's most frequently abused drug, the difference between imipramine (1.6 ± 2.1) and placebo (3.3 ± 3.2) (effect size = 0.64), ($F = 5.38$, 76 df, $p < 0.03$), is less robust, although still significant. F tests reported are for main effect of medication, in an analysis of covariance (ANCOVA) with the baseline level of the dependent measure entered as a covariate. For each patient, the proportion of urines negative for all drugs (by EMIT assay) during the last 4 weeks of the study was calculated and treated as a continuous measure. There was no difference between imipramine (0.47 ± 0.41) and placebo (0.44 ± 0.41) in the proportion of drug-negative urines.

This preliminary analysis suggests that imipramine exerts a strong antidepressant effect in carefully selected methadone patients, but that its effect on illicit drug use is less robust, being manifest in self-report, but not in the urine-based measure. Replication is indicated with quantitative urinalysis, which might provide an objective measure of reduced drug use short of abstinence.

CONCLUSIONS

This chapter reviewed both the literature and the authors' recent studies bearing on the hypothesis that depression can be treated in patients with substance use disorders and that such treatment will improve the outcome of substance abuse. The literature actually covers a large number of placebo-controlled trials in which various antidepressant medications were tested as treatments in clinical populations with substance use disorders. These include studies of several antidepressants and lithium in alcoholic samples, of antidepressants in samples with cocaine abuse, as well as samples with opiate dependence.

As a whole, the literature is inconclusive on the question of whether treatment of depression is effective in such populations. Many of the studies selected depressed patients on the basis of cross-sectional mood scales rather than clinical history and syndromal diagnosis, which may have resulted in samples replete with transient, substance-induced mood syndromes or adjustment reactions to stress rather than true mood disorders. The result is high placebo response rates and little or no medication effect. Other studies, including those of cocaine abusers, were not designed to treat depression, but to test whether the medication had any direct effect on drug use behavior.

The authors and colleagues, seeking to fill the gap in the literature, are conducting a series of studies in substance abusers with depression diagnosed by clinical interview, using criteria designed to select patients with primary or chronic depression. Pilot studies in depressed outpatient alcoholics and in depressed methadone maintenance patients, as well as preliminary analysis of a large trial in methadone patients, suggest that depression can be identified in substance abusers and that it responds robustly to standard antidepressant medication treatment. There is also evidence of a beneficial effect on substance use itself, although this appears to be less robust and further study is needed to determine its true extent.

These findings have theoretical implications for the relationship between substance use disorders and depression (see table 1), suggesting that the disorders are at least in part independent. Depression can be identified and treated, and substance use may be reduced, but in most cases it does not vanish as one would predict were a patient taking drugs purely to self-medicate. Instead, depression is probably only one of several factors that contribute to the onset or maintenance of an addiction. It is also possible that mood disorders are responsible for initiation of drug use, but that the drug use itself is so rewarding that it takes on a life of its own.

In terms of clinical implications, the conclusion that pure self-medication is rare does not diminish the importance of identifying and treating depression as part of a comprehensive plan of addiction treatment. Even if depression and addiction are entirely independent disorders, depression carries its own associated morbidity and mortality (Murphy et al. 1992). There is ample evidence that psychopathology is associated with poor prognosis for substance abuse. The effect of ameliorating these symptoms on prognosis of drug abuse requires further study.

Future Directions

These findings suggest several future directions for research. There are still relatively few well-designed studies of the treatment of comorbid psychiatric disorders in substance-dependent patients. The older studies, as noted, tended to have methodologic limitations. Recent studies on treatment of depression (Mason and Kocsis 1991; Nunes et al. 1993), as well as a recent series on buspirone in anxious alcoholics (Malcolm et al. 1992; Tollefson et al. 1990; Kranzler et al. 1994), suggest that the strategy of identifying and treating psychiatric comorbidity in substance abusers is worth pursuing.

Several replication-extensions of the recent work might be considered with other antidepressant agents, other comorbid mood or anxiety disorders, and other substance use disorders. Several examples follow.

- Newer antidepressant agents: Most trials to date have involved tricyclic antidepressants. Trials with newer agents, such as specific serotonin uptake inhibitors, seem worthwhile because these may have fewer side effects and a greater margin for safety, or exert a stronger effect on depression or substance abuse or both.

- Depressed cocaine abusers: Given the inconsistent results of desipramine trials in unselected cocaine abusers, a trial of desipramine in selected depressed cocaine abusers would be useful. No such trial has been reported to date.

- Psychotherapy of depression: Recently developed short-term psychotherapy methods, cognitive therapy (Wright 1988; Elkin et al. 1989; Klein and Ross 1993), and interpersonal psychotherapy (Klerman et al. 1984; Elkin et al. 1989; Klein and Ross 1993) have demonstrated some efficacy in the treatment of depression. These warrant testing as alternatives to pharmacotherapy in depressed substance abusers because of concerns about the risks of medication interactions with illicit substances.

- Combined pharmacotherapy and psychotherapy: The literature suggests that effective antidepressant medication treatment in depressed substance abusers only partially reduces the drive to use drugs or alcohol. This suggests that antidepressants might best be applied as part of a multifaceted treatment strategy. For example, antidepressants could be studied in combination with promising techniques such as cognitive-behavioral therapy (Woody et al. 1983), relapse prevention (Carroll et al. 1991; Daley and Marlatt 1992; Marlatt and Gordon 1985; McAuliffe and Chi'en 1986; Rawson et al. 1991), cue extinction (Childress et al. 1992), or contingency management (Higgins et al. 1993; Iguchi et al. 1988; Stitzer et al. 1992). A two-way factorial design is possible, crossing two levels of medication (placebo, antidepressant) with two levels of therapy (standard versus enhanced intervention). An elegant example of such a study in cocaine abusers not selected for depression has recently been published (Carroll et al. 1994).

A second important line of research would focus on improving methods of identifying "true" depression in substance abusers, including those who may still be actively using. Certainly, the ideal method is to conduct a psychiatric diagnostic interview after at least 2 to 4 weeks of abstinence. However, the ideal is often difficult to achieve. Many patients will have difficulty abstaining as outpatients, and inpatient stays may not be available to uninsured patients, for example, or too short to be useful, even with insurance. In addition, some patients will decline hospitalization for legitimate reasons such as work or family responsibilities.

Hypothesizing that features of the clinical history can be used to identify treatable depression, the authors have developed a special version of the Structured Clinical Interview for DSM, the SCID-Substance Abuse Comorbidity (SCID-SAC) (Nunes et al., in press), which elicits these features. They include whether the depression antedated the onset of substance abuse, whether it persisted during historical periods of abstinence (such as during an episode of successful treatment or a stint in jail), and the extent to which the depression is chronic or longstanding. Rounsaville and colleagues (1991) suggest that depression emerging during a period of stable substance use may be a valid criterion for selecting "true" depression. Hasin and colleagues have developed a highly detailed structured interview, the PRISM (Hasin et al. 1994), which elicits a number of historical features connecting substance use to comorbid mental disorders. Further study of the reliability and predictive validity of such historical features and of instruments such as the SCID-SAC and PRISM are needed. Clearly, better tools for sample selection will improve the power and precision of clinical trials of antidepressant agents in substance abusers.

Research should also be considered on biological tests that might aid in diagnosis. Unfortunately, biological tests for depression, such as the dexamethasone suppression test (DST), are still of very limited use, and lack sensitivity and specificity. The extensive literature on the DST in substance abusers (Kroll et al. 1983; Willenbring et al. 1984; Ravi et al. 1984; Khan et al. 1984; Abou-Saleh et al. 1984; Newsom and Murray 1983; Johnson and Perry 1986; Burch et al. 1986; Dackis et al. 1984, 1986; Zern et al. 1986), for example, shows that the DST is influenced by recent substance use, and therefore it is not very useful in distinguishing depression. However, better tests may become available. In addition, a nascent literature suggests that physiologic challenge with sodium lactate infusion (Baron et al. 1990; Cowley et al. 1989; George et al. 1989) may have promise for identifying panic disorder in alcoholics.

Finally, a number of research questions exist in the realm of services. If the approach to diagnosing and treating depression and other comorbid mental disorders is applied in drug treatment clinics in the community, what are the risk-benefit and cost-effectiveness ratios? Do the benefits outweigh the risks? How can a diagnostic-therapeutic enhancement be delivered efficiently, at a low enough cost to justify what may be marginal improvements in outcome? For example, having an experienced psychiatric diagnostician interview all patients admitted to a substance use clinic and follow those with suspected comorbidity requires a substantial amount of

the time of an expensive staff member. Could regular counselors use screening instruments to do the case finding during their routine contacts with patients? Answering this question calls for a straightforward design comparing the sensitivity and specificity of counselors' screenings, of different screening instruments instead of gold standard psychiatric interview, and the time and cost of the approaches.

Designs addressing risk-benefit and cost-effectiveness of treatment interventions are more problematic and require further methodologic development. The crux of the problem is that long-term treatment and followup are needed, but it is ethically difficult to justify randomizing depressed patients, for example, to a placebo control condition for 6 to 12 weeks when acute efficacy studies suggest that the depression would respond to treatment. Quasi-experimental designs, with careful attention to identifying and minimizing potential biases in nonrandomized control conditions, may be needed.

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The Course and Treatment of Substance Use Disorder in Persons With Severe Mental Illness

Kim T. Mueser, Robert E. Drake, and Keith M. Miles

There is now a widespread acceptance that persons with severe mental illness are at increased risk to develop substance use disorders (alcohol and drug abuse/dependence). Reviews of the prevalence of substance use disorders in clients with schizophrenia (Mueser et al. 1990), bipolar disorder (Goodwin and Jamison 1990), and the young, chronically mentally ill (Safer 1987) indicate a wide range of prevalence estimates, from as low as 10 percent to over 65 percent. Variability in prevalence rates can be attributed to differences across studies in factors such as the setting in which clients are sampled (e.g., community mental health center, acute inpatient, chronic inpatient), methods for assessing psychiatric and substance use disorders (e.g., structured clinical interview, chart review), and the demographic mix of the study sample (e.g., proportion of males) (Galanter et al. 1988; Mueser et al. 1995).

Despite the variability in prevalence estimates, strong evidence indicates that the rate of comorbid substance use disorders in people with severe mental disorders is substantially greater than in the general population. The most compelling evidence supporting this is provided by the Epidemiological Catchment Area (ECA) study (Regier et al. 1990), which assessed psychiatric and substance use disorders in over 20,000 persons living in the community and in various institutional settings. The results of this study indicated that persons with a psychiatric disorder were at increased risk for developing a substance use disorder over their lifetime. Of particular importance, people with severe mental illness were especially vulnerable to substance use disorders. For example, those with schizophrenia were more than four times more likely to have had a substance use disorder during their lifetime than persons in the general population, and those with bipolar disorder were more than five times as likely to have such a diagnosis.

The high rate of substance use disorders among persons with severe mental illness has important clinical implications, because their substance

abuse is associated with an array of negative outcomes. Common negative consequences include increased vulnerability to relapses and rehospitalizations, greater depression and suicidality, violence, housing instability and homelessness, noncompliance with medications and other treatments, increased vulnerability to human immunodeficiency virus (HIV) infection, increased family burden, and higher service utilization and costs (Bartels et al. 1993; Clark 1994; Bartels et al. 1992; Cournos et al. 1991; Drake et al. 1989; Yesavage and Zarcone 1983). However, evidence also suggests that as dual-diagnosis clients attain stable remission, their vulnerability to these negative outcomes lessens (Bartels et al. 1993; Zisook et al. 1992). Thus, interventions that are successful at reducing substance abuse in clients with severe psychiatric disorders may also confer positive benefits in such areas as symptomatology, community functioning, service utilization, and costs of treatment.

In this chapter the authors begin with a discussion of issues in the assessment of substance use disorders in persons with severe psychiatric disorders. Following this, an overview provides a natural history of substance use disorders in both the general population and among the chronically mentally ill. Next, the failure of the parallel treatment system for dually diagnosed clients is briefly reviewed, followed by a description of more recently developed integrated substance abuse and mental health methods. Preliminary data are then presented from a 3-year study by the New Hampshire-Dartmouth Psychiatric Research Center of integrated treatment for dual-diagnosis clients. The implications of research on integrated treatment approaches for policy decisions are discussed in a concluding section, as are future directions for research in this area.

ASSESSMENT

Several common difficulties arise when assessing substance disorders among persons with severe mental illness (Drake et al. 1993*a*; Drake and Mercer-McFadden 1995; Stone et al. 1993). The most common problem is that mental health clinicians often do not obtain a thorough history of substance use (Ananth et al. 1989). Even when interviewed thoroughly, however, persons with dual disorders are subject to the usual problems of denial, distortion, and minimization that attend self-reports of substance use, especially the use of illicit drugs, in the general population (Aiken 1986; Galletly et al. 1993; Stone et al. 1993). Psychiatric clients are also prone to individual distortions arising from the cognitive, emotional, and other aspects of their mental illness (Mueser et al. 1992).

Another important factor that complicates assessment is the fact that the usual dimensions of substance abuse—pattern, consequences, dependence syndrome, and subjective distress—are qualitatively different in substance abusers who have mental illness compared to those who do not (Drake et al. 1990; Lehman et al. 1994; McHugo et al. 1993). Specifically, compared with non-mentally ill substance abusers, those with dual disorders use lower amounts of alcohol and drugs, experience different consequences, are less likely to develop a dependence syndrome, and have less subjective distress. For example, the typical consequences of substance abuse among people with a mental disorder are difficulties with money management, destabilization of illness, unstable housing, and inability to participate in rehabilitation, but not with the items on the Michigan Alcohol Screening Test (Selzer 1971) or the Alcohol Dependence Scale (Skinner and Horn 1984). Standard instruments, such as the Addiction Severity Index (McLellan et al. 1980), are relatively insensitive to clinically important levels of abuse among persons with psychiatric disorders.

One last but critical problem is that dual-disordered clients are typically in a premotivational state regarding their substance abuse, even if they are well engaged in mental health treatment (Drake et al. 1990). To be useful for treatment planning and monitoring, assessment instruments must be sensitive to stages of motivation and to changes that occur prior to attaining abstinence. The authors and others, thus, recommend the use of multiple tests (Carey, this volume; Drake et al. 1990), multimodal testing (Stone et al. 1993), and an explicit assessment of the stage of treatment (McHugo et al. 1995). Furthermore, there is a need to develop new instruments sensitive to the presence of substance use disorders in the population of persons with severe psychiatric disorders (Drake et al. 1993*a*; Lehman et al. 1993*b*).

NATURAL HISTORY OF SUBSTANCE USE DISORDERS

As a backdrop to understanding the longitudinal course of psychiatric and substance use disorders, it is helpful to review what is known about the course of primary alcohol and drug use disorders. Vaillant's (1983) seminal work on the natural history of alcoholism provides compelling evidence that for most clients the disorder is lifelong and is associated with a substantial risk for early mortality. Despite the overall negative (and often progressively negative) long-term outlook for alcoholics, a cumulative proportion of individuals achieve abstinence, even in the absence of professional treatment. Vaillant (1983) estimated that

approximately 3 percent of alcoholics become abstinent each year without the benefit of formal treatment programs, and between 1 and 2 percent of abstinent alcoholics resume social drinking. Although the efficacy of treatment for alcoholism continues to be debated, Vaillant (1983) estimated that treatment of alcoholics increases their recovery rate to approximately 6 percent yearly.

Fewer data are available on the longitudinal course of primary drug use disorders, although in general the findings are compatible with those reported by Vaillant (1983) for alcoholism (Vaillant 1973, 1988; Simpson et al. 1986). In one of the largest and longest longitudinal studies published to date, Hser and associates (1993) reported 24-year outcomes for 581 narcotics addicts who had been admitted to the California Civil Addict Program between 1962 and 1964. Data on the long-term outcome of these patients' drug use disorders revealed high mortality rates and a rate of spontaneous remission in the absence of treatment that was somewhat lower than that reported by Vaillant (1983) for alcoholics. At the end of the followup period, 28 percent of the sample were dead, and only 19 percent had attained stable abstinence, which was defined as not using drugs for the prior 3 years.

Interpretation of the negative long-term outcome for the Hser and colleagues' (1993) study should to be tempered by recognition that the sample probably represented a more severely ill group of drug abusers than the alcoholics studied by Vaillant (1983). For example, the narcotics addicts studied by Hser and associates (1993) met criteria for a drug use disorder at an early age and were involved the legal system. Despite differences across longitudinal studies in sample characteristics, research on the natural course of primary alcohol and drug use disorders indicates that these disorders are usually chronic over a lifetime. There is considerable variation in clients' substance use behavior over time, but relatively few spontaneously attain stable abstinence, and clients are at increased risk of early mortality. Although the available evidence indicates that substance use disorders are relatively chronic over the lifetime, illicit drug use is not. Recent epidemiological surveys indicate that most people in the United States cease using illicit drugs by the age of 30 and that heavy drinking declines at around the same age range (Chen and Kandel 1995). It appears that substance use disorders tend to be chronic over long periods of time, but that alcohol and drug use behavior in the nonabusing population tends to decline with age over time.

Very little research has examined the natural history of substance use disorders in people with severe mental illnesses. However, the available data suggest that the outcome of dually diagnosed persons who receive services from the traditional parallel treatment system is bleak. Several prospective studies have shown increased rates of hospitalization over 1 year for psychiatric clients with a substance use disorder (Drake et al. 1989; Osher et al. 1994). Furthermore, in one study even minimal levels of drinking, not considered abuse by clinicians, predicted rehospitalizations (Drake et al. 1989). One-year followup studies also show little remission of substance use disorder (Drake et al. 1996). In line with the evidence indicating that substance abuse frequently precipitates disruptive behavior, symptom exacerbations, and rehospitalizations, researchers in the McKinney demonstration project on homeless mentally ill adults concluded that substance use disorders were the single most important factor contributing to housing instability in this population (Center for Mental Health Services 1994).

In perhaps the longest longitudinal study of dually diagnosed persons, Bartels and colleagues (1995) conducted followup assessments 7 years after an initial evaluation on 148 out of 170 (86 percent) severely mentally ill clients. At baseline, 24 percent of the sample had an alcohol use disorder, and at followup 21 percent had such a disorder, a nonsignificant difference. Similarly, the rate of drug use disorder also did not change significantly from baseline (20 percent) to followup (17 percent). Despite these essentially negative findings, some clients were successful in becoming abstinent from substance use. Over the 7 years, 25 percent of the clients with an alcohol use disorder and 35 percent clients with a drug use disorder at initial evaluation achieved abstinence. Furthermore, clients with substance abuse diagnoses were more likely to attain abstinence than those with substance dependence diagnoses.

The lack of change in the overall rate of substance use disorders across the two assessments of the Bartels and colleagues (1995) study reflects the fact that some clients who did not meet criteria for a substance disorder at the baseline assessment met the criteria at followup. Indeed, in two separate samples, Drake and Wallach (1993) found that clients with severe mental illness but who appeared to be moderate, nonabusive drinkers were likely to develop alcoholism over several years. This finding is also consistent with Cuffel and Chase's (1994) analysis of the stability of substance use disorders over 1 year in persons with schizophrenia. Thus, dual-diagnosis clients tended to recover from substance use disorders at very slow rates, although there is considerable

fluctuation in and out of the disorder among those who are moderate users and those with abuse rather than dependence.

In summary, most clients with a primary alcohol or drug use disorder have a chronic course of illness, with the actual substance use behavior varying greatly over time and a small percentage of people attaining stable abstinence each year (i.e., less than 5 percent per year). In addition to the financial and psychosocial consequences associated with substance use disorders, these clients are also at increased risk for early mortality. The small amount of information currently available about the natural history of dually disordered clients suggests a similar picture, complicated by an increased risk for disruptive behavior, hospitalizations, and psychosocial problems.

INTEGRATED TREATMENT

By the late 1980's it had become increasingly clear that the traditional approach of treating dually diagnosed clients through separate mental health and substance abuse service systems was inadequate for persons with severe psychiatric disorders. A wide range of problems occurred with the parallel and sequential approach to treating comorbid psychiatric and substance use disorders (Minkoff and Drake 1991; Polcin 1992; Ridgely et al. 1987, 1990). For example, parallel treatment approaches tended to breed mistrust between those professionals whose primary focus was on mental illness and those working mainly with substance use disorders, with comorbid clients falling between the cracks of the system (Sellman 1989). Furthermore, because professionals were unaware of how to combine psychiatric and substance abuse services effectively, the burden of integrating the disparate messages of the two systems fell entirely on clients, who were ill-equipped to handle such a task. Finally, a wealth of evidence documents that traditional methods for treating primary substance use disorders are ineffective at meeting the needs of clients with heterogeneous psychiatric disorders (Baekeland et al. 1973; LaPorte et al. 1981; McLellan et al. 1983; Rounsaville et al. 1987; Woody et al. 1990). Thus, the poor outcome of these clients appears to stem from barriers within the traditional service system in which mental health and substance abuse services have separate and parallel programs, staff training, models of treatment and recovery, and funding streams (Ridgely et al. 1990).

In light of the poor outcome for dually diagnosed persons treated in parallel or sequential treatment systems, programs serving the severely mentally ill have moved towards integrating substance abuse and mental health treatment into comprehensive programs (Carey 1989; Drake et al. 1993*c*; Nikkel and Coiner 1991; Minkoff 1989; Ziedonis and Fisher 1994). Several different integrated treatment models have been developed (reviewed in Lehman and Dixon 1995; Minkoff and Drake 1991), and, despite differences across programs, all integrated treatment approaches share some common principles.

At the most basic level, integrated treatment means that both mental health and substance abuse treatments are simultaneously (not sequentially) provided by the same person, team, or organization. In addition, most models include case management, group interventions (e.g., persuasion groups, social skills training), assertive outreach to engage people in treatment and to address pressing social or clinical needs, education about substance abuse and mental illness, focus on the motivational aspect of treatment (e.g., persuading clients to address alcohol- or drug abuse-related issues by identifying personal goals that are incompatible with continued substance use), and endorsement of a long-term perspective (rather than time-limited treatment). Furthermore, many, but not all, approaches utilize behavioral strategies for helping clients cope with urges to use substances and resist social overtures to use drugs or alcohol, work closely with patients' families and other members of their social network, and employ "stage-wise" treatment to ensure optimal timing of clinical interventions. For example, the New Hampshire integrated treatment model (Drake et al. 1993*c*) posits that recovery from substance use disorders progresses through four different stages, each with different goals and interventions: engagement (establishing a therapeutic relationship with the patient), persuasion (motivating the patient to address substance abuse), active treatment (working directly to reduce substance use behavior), and relapse prevention (developing strategies to reduce vulnerability to relapses). Table 1 summarizes the common ingredients of many integrated treatment programs and the function of each ingredient.

RESEARCH ON INTEGRATED TREATMENT

Studies of integrated treatment programs have been limited by small sample sizes, brief followup periods, measurement problems (e.g., failure

TABLE 1. *Common ingredients of integrated mental health and substance abuse treatment programs.*

Ingredient	Function
The same professionals provide mental health and substance abuse treatment	Coordinating mental health and substance abuse treatments; avoiding sending "mixed messages" or failing to treat relevant problem areas
Case management	Attending to the range of clinical, housing, social, and other needs that may be affected by either substance abuse or mental health problems
Assertive outreach	Providing services directly in the community to engage patients, address pressing needs, followup and reengage relapsing patients
Group interventions	Providing peer support, persuading patients to address substance use behavior, promoting sharing of coping strategies for managing urges to use substances and for social situations
Education about substance abuse and mental illness	Informing patients about the nature of their psychiatric disorders and the effects of substance abuse to highlight negative effects of drugs and alcohol
Motivational techniques	Engaging patients in working towards substance use reduction and abstinence by identifying personally relevant goals that become a focus of treatment

TABLE 1. *Common ingredients of integrated mental health and substance abuse treatment programs (continued).*

Ingredient	Function
Behavioral strategies	Using techniques such as social skills training, training in coping skills to manage symptoms and high risk situations, and relapse prevention to reduce substance use and vulnerability to relapses
Family/social network factors	Working with members of patient's social networks to reduce factors that may maintain substance use behavior, help patients progress towards personal goals, and bolster resistance to relapses
Stage-wise treatment	Providing specific interventions based on the patient's specific stage of recovery: engagement, persuasion, active treatment, or relapse prevention
Long-term perspective	Recognizing that dual disorders are chronic conditions that require long-term, not time-limited, intervention

to employ standardized instruments to assess diagnosis or substance abuse), and lack of experimental design. While a comprehensive survey of the integrated treatment research is beyond the scope of this chapter (for a review, see Drake et al., in press), a brief synopsis of progress in this area can be provided.

Early uncontrolled studies of integrated treatment showed decreased hospital use and substance abuse among clients who remained in treatment. Hellerstein and Meehan (1987) found that 10 men with

substance use disorders and schizophrenia who participated in a weekly outpatient group had decreased hospital use over 1 year compared to such use before treatment. Kofoed and associates (1986) treated 32 dually diagnosed clients in outpatient groups with a focus on substance abuse. The 21 clients who continued to abuse drugs or alcohol dropped out of treatment, whereas the 11 clients who remained in the program for at least 1 year reduced their substance use and had lower rates of hospital utilization. Ries and Elingson (1989) found that 12 of 17 dual-diagnosed clients who attended integrated treatment groups as inpatients reported they were abstinent 1 month after discharge.

Bond (1989) reported that 56 severely mentally ill persons with co-occurring substance abuse had decreased hospital use during 1 year of intensive case management that addressed both substance abuse and mental health issues. More recently, Durell and colleagues (1993) reported on the outcomes of 84 severely mentally ill clients, of whom 43 (51 percent) were also substance abusers, followed in intensive case management for at least 18 months. For all clients, 76 percent showed increased community tenure and increased use of formal and informal community resources, and two-thirds of the dually diagnosed clients had reduced substance abuse at followup.

A significant step forward occurred with the Community Support Program (CSP) demonstration project. This project involved 13 exploratory studies funded by the National Institute of Mental Health that were conducted between 1987 and 1990. These programs targeted several high-risk groups with dual disorders, including inner-city residents, minorities, women with children, and migrant farmworkers. The studies were limited by the relatively brief followup period (12 to 18 months) and the fact that only two programs had control groups (Bond et al. 1991; Lehman et al. 1993*a*).

The outcomes from the 13 projects were recently reviewed by Mercer-McFadden and Drake (1995). The general findings can be summarized as follows: (1) all programs were successful in engaging clients in outpatient dual-diagnosis services; (2) engagement in outpatient-based services generally led to decreased utilization of inpatient and institutional services; and (3) there was minimal reduction in substance abuse over 1 year, although the interpretation of results was complicated by measurement difficulties (e.g., failure to employ instruments sufficiently sensitive to changes in substance use in the mentally ill population). Despite the limitations of these pilot studies, they provide initial encouragement and support for the notion that

integrated mental health and substance abuse services are required for clients with dual disorders.

Jerrell and Ridgely (1995) have recently reported results similar to those found in the CSP demonstration projects. They followed 147 dually diagnosed clients receiving one of three forms of integrated treatment (case management, cognitive-behavior therapy, or a modified 12-step approach) over a 12- to 18-month period. Interviewer ratings indicated modest improvements in the areas of work, independent living, immediate and extended social relationships, self-reported satisfaction with work and family relationships, and psychiatric symptoms. Other areas of social adjustment did not change (e.g., work or family adjustment), and neither did the overall rate of alcohol symptoms, alcohol use, or drug use. Furthermore, there was no change in number of days hospitalized, although there was a decrease in emergency visits that accompanied an increase in medication and outpatient visits.

The potential benefits of integrated treatment are also supported by a study in Washington, D.C., that was recently completed by the New Hampshire-Dartmouth Psychiatric Research Center (Drake et al. 1993*d*). In this study, 172 homeless persons with major mental illness plus substance disorder were randomly assigned to one of two forms of intensive case management: cognitive-behavioral case management, which focused on training skills that would enable clients to cope with urges to use substances and skills for resisting use in social situations, or social network case management, which focused on working with clients' social networks to enhance their ability to support abstinence as a therapeutic goal for the client. A matched comparison group of 67 homeless dually diagnosed persons received usual community services. Both experimental groups showed positive results in terms of decreased hospitalizations and homelessness, increased stable community housing, and decreased substance abuse over 18 months. Results favored the experimental groups over the matched comparison group, but marked differences did not appear to distinguish the two experimental groups (Drake et al., under review).

A common limitation of much of the research on integrated treatment has been relatively brief followup periods (i.e., 18 months or less). One descriptive study found benefits for integrated treatment when it was provided over a significantly longer time interval (Drake et al. 1993*e*). Eighteen persons with schizophrenia and alcoholism received integrated treatment over 4 years in a program that included case management and

dual-diagnosis groups. By the end of the followup period, 11 clients (61 percent) had achieved stable abstinence (i.e., had not abused for 6 months). These results underscore the importance of providing integrated treatments that extend over relatively long periods of time (e.g., Durrell et al. 1993).

Despite the lack of controlled studies, the weight of the evidence on the effects of integrated treatment from some 30 studies is overwhelmingly positive (Drake et al., in press). However, there is still a need for systematic, longer-term studies to quantify the effects of integrated treatments provided over several years. The preliminary results of one such study conducted by the New Hampshire-Dartmouth Psychiatric Research Center are described below.

THE NEW HAMPSHIRE DUAL DISORDERS STUDY

This study compared the effects of two different case management methods for providing integrated treatment to clients with dual disorders: intensive case management teams based on the Assertive Community Treatment model (Stein and Test 1985) with clinician caseload ratios of 1 to 10 versus regular case management teams with ratios of 1 to 30. Both models included outreach, team orientation, integrated dual-diagnosis treatment, a longitudinal approach, and supportive housing. A total of 240 clients were recruited into the study, with followup data available for 215. At entry to the study all clients met criteria for major mental illness (schizophrenia, schizoaffective disorder, or bipolar disorder) plus recent substance use disorder (within the past 6 months). Clients were randomly assigned to one of the two integrated treatment programs in which they received treatment and were routinely assessed over 3 years. The characteristics of the sample are summarized in table 2.

A comprehensive array of assessments was conducted at regular intervals of clients in both programs, including substance use behavior, symptoms, quality of life, and service utilization. The results of selected outcome measures are presented here. Alcohol and drug use disorders were rated by research staff using clinician rating scales (Drake et al. 1990) in which a 1 corresponds to no substance use, 2 refers to substance use but not abuse, 3 is substance abuse, and 4 and 5 are substance dependence.

TABLE 2. *Demographic and diagnostic characteristics of patients.*

Characteristic	Mean	(SD)
Age	35.6	(8.5)
	Number	(%)
Sex		
Male	161	(75)
Female	54	(25)
Race		
White	204	(95)
Black	5	(2)
Native American	4	(2)
Asian	1	(0.5)
Hispanic	1	(0.5)
Marital status		
Never married	135	(63)
Married	15	(7)
Separated	8	(4)
Divorced	55	(25)
Widowed	2	(1)
Employment status		
Unemployed	183	(85)
Sheltered employment	18	(8)
Competitive employment	14	(7)
Psychiatric diagnosis		
Schizophrenia	108	(50)
Schizoaffective	50	(23)
Bipolar	51	(24)
Delusional disorder	6	(3)
Current substance use disorder		
Alcohol abuse/dependence	96	(45)
Drug abuse/dependence	28	(13)
Alcohol and drug abuse/dependence	59	(27)
Alcohol or drug abuse/dependence in remission	32	(15)

Stage of treatment was rated with the Stage of Treatment Scale (McHugo et al. 1995). For this scale, 1 and 2 correspond to the engagement phase, 3 and 4 are the persuasion phase, 5 and 6 are the active treatment phase, and 7 and 8 are the relapse prevention phase. Days of drug use and days of drinking to intoxication in the past 6 months were assessed using the timeline followback method (Sobell et al. 1988).

Global adaptive functioning was assessed with the Global Adjustment Scale (GAS) (Endicott et al. 1976), which ranges between 0 and 100 with higher numbers indicating better functioning. Symptoms were rated using the expanded version of the Brief Psychiatric Rating Scale (Lukoff et al. 1986). For the data presented here, the number of symptoms rated greater than 4 (moderate severity) was summed to form an overall index of symptom severity. Overall life functioning (OLF) was rated on a 5-point scale (1 to 5) developed for the project, and the OLF ratings were based on changes from baseline in living situation (e.g., time in the hospital, jail, homeless), symptom severity, participation in activities in the community (e.g., school or work), and social contacts (e.g., visits or telephone calls with family members or friends). Each client began with a 3 rating at baseline, with lower ratings at subsequent assessments reflecting a worsening in OLF and higher ratings reflecting improvements in OLF. Satisfactory levels of interrater reliability were established for all measures.

Preliminary analyses indicate that both programs were effective in ameliorating or decreasing substance abuse and in improving other outcomes, and the differences between the two programs are currently being examined. The changes in the outcome measures described above and days in the hospital during the 3 years are depicted in figures 1 and 2 for the combined treatment groups, including clients who dropped out of treatment but were followed for 3 years.

Inspection of the figures suggests that the integrated treatments resulted in significant reductions in hospitalization in the first year of the study and that global improvements were evident throughout the 3 years in both substance abuse and other areas of functioning. As evident from the Stage of Treatment Scale, most of the clients moved steadily through motivational stages of treatment. In fact, by the end of the 3-year followup, approximately half of the clients had attained some degree of abstinence, a substantially higher proportion than would be expected from studies of

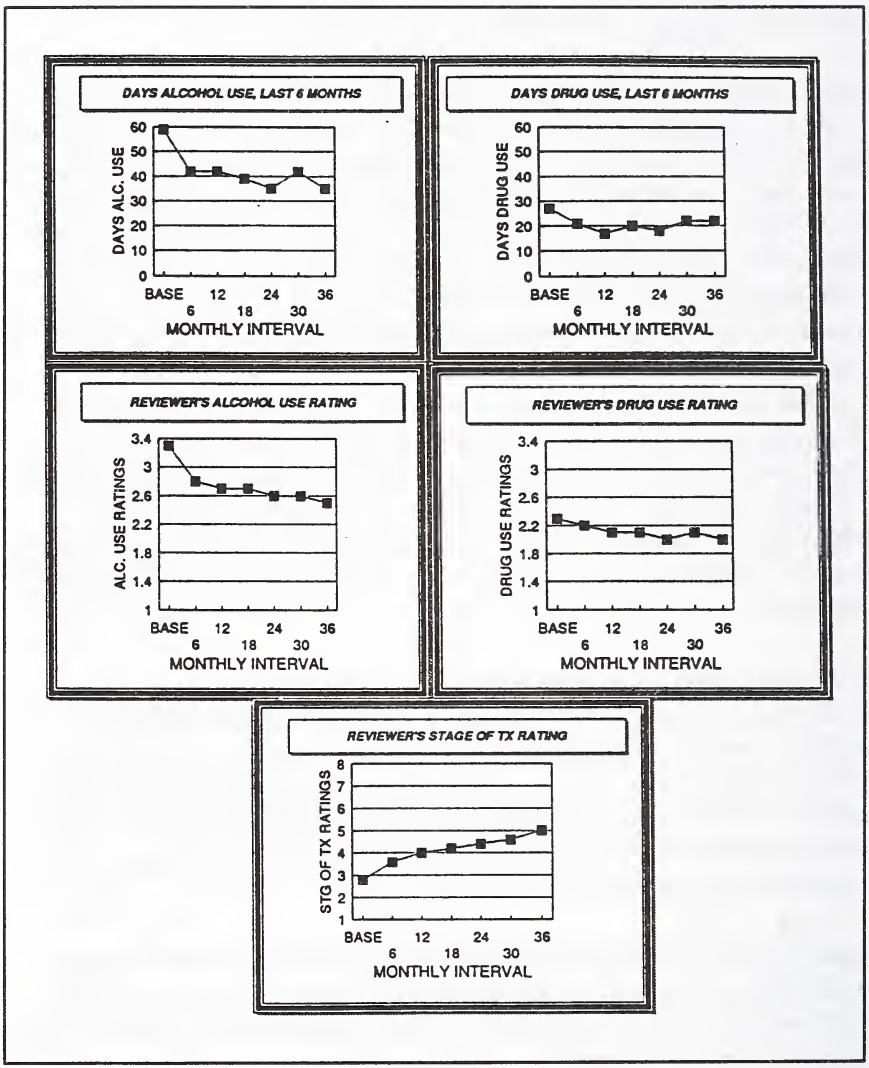

FIGURE 1. *New Hampshire-Dartmouth Psychiatric Research Center dual diagnosis study: Alcohol and drug use (N = 215).*

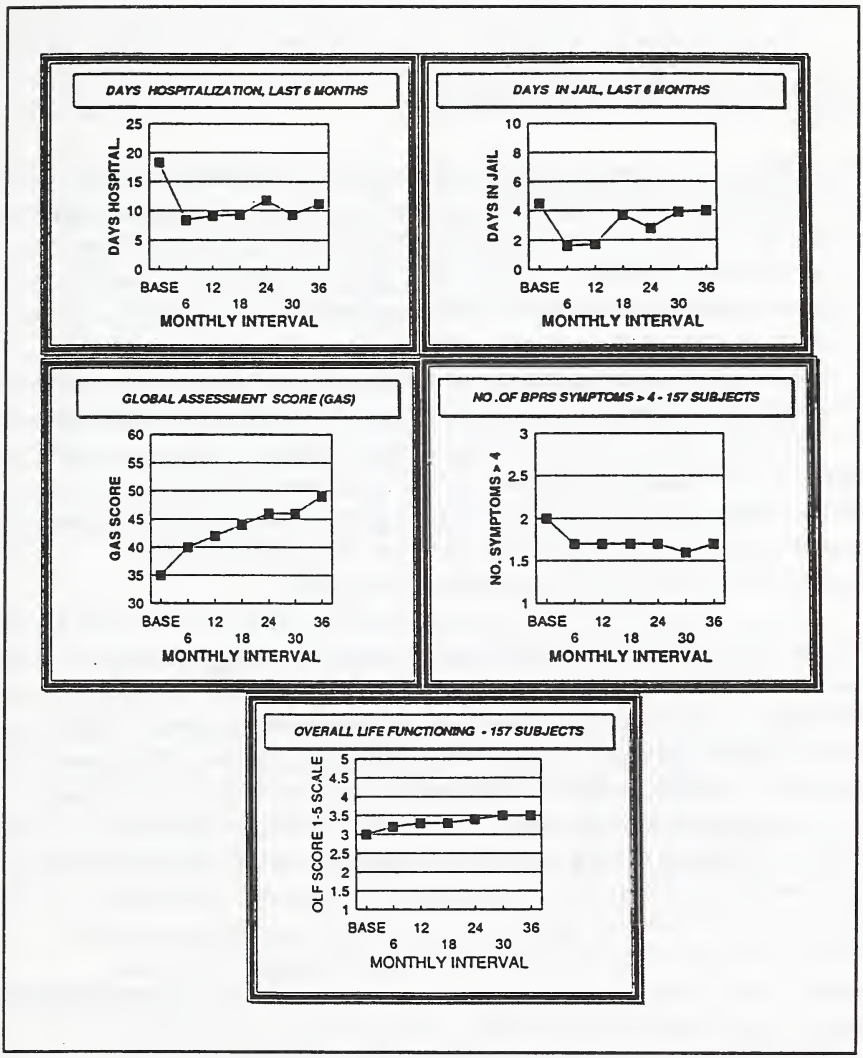

FIGURE 2. *New Hampshire-Dartmouth Psychiatric Research Center dual diagnosis study: Clinical and service utilization measures (N = 215).*

the natural course of dually disordered clients (Bartels et al. 1995). These generally very positive results, while preliminary, provide additional support for the beneficial effects of integrating substance abuse and mental health treatments for the population of severely ill psychiatric clients.

DISCUSSION AND CONCLUSIONS

The profoundly negative impact of substance abuse on the course of severe psychiatric disorders has become a major focus of attention, and a concerted effort over the past decade to improve the outcomes of these clients has already begun to pay off. Longitudinal research on the course of dual disorders in clients who received treatment from the traditional parallel service system indicated a very slow rate of recovery, with usually less than 5 percent becoming abstinent each year. Growing discontentment with the parallel treatment approach rapidly led to the development of a different, broad-based model that seeks to improve outcomes by integrating mental health and substance abuse treatments. Preliminary studies employing a range of different integrated treatment models have yielded promising results that suggest better outcomes than those traditionally produced by the parallel service system.

Despite the hopeful findings of these studies, many questions remain unanswered about integrated treatment. One thorny issue has been the difficulty of comparing parallel and integrated treatment programs. Most of the evidence supporting integrated treatment programs is derived from either noncontrolled studies that followed the progress of a group of clients who received integrated treatment, or controlled studies comparing the efficacy of different models of integrated treatment. Direct comparisons of integrated and parallel treatment approaches have proved impossible to study because of treatment drift; as soon as clinicians providing parallel treatment become aware that mental health and substance abuse interventions can be integrated, they begin to do so, thereby compromising their fidelity to the parallel services model. For this reason, it is not clear whether controlled research will ever be conducted that definitively demonstrates the superiority of integrated treatments over parallel ones, although integrated treatment is rapidly becoming the status quo.

Another question concerns the effects of group interventions for dually diagnosed clients. A number of different group interventions have been described, with foci ranging from persuasion (Noordsy and Fox 1991),

problemsolving (Carey et al. 1990), and social skills training (Nikkel 1994) to broad-base supportive/education/skills building (Hellerstein and Meehan 1987). Although group treatment is a common ingredient in many integrated programs, no consensus exists as to the optimal format, content, or goals of these groups. Research is needed to evaluate the benefits of different approaches to group treatment for dually diagnosed clients and to explore whether certain clients are likely to gain more from a particular group format.

A final question concerns the comparative efficacy of different integrated treatment models. Thus far, the evidence suggests that different approaches to providing integrated treatment for dually diagnosed clients result in similar rates of improvement (Jerrell and Ridgeley 1995; Drake et al., under review). These results, if supported by other ongoing research, could have important policy implications. If different treatment programs result in comparable benefits, then the adoption and dissemination of integrated treatments should perhaps be determined by ease of implementation and cost. Of related importance, the determination of which clients benefit from which programs (or program components) could also have implications for tailoring treatment to best suit the needs of individual clients.

There have been tremendous strides in the past 10 years in the development of effective interventions for persons with dual disorders. The results of research conducted thus far provide grounds for cautious optimism. At the same time, there is still much work to be done to help clients recover from the double handicap of mental illness and substance use disorder. The significant advances made in the past decade by professionals, working in collaboration with clients and their families, auger well for improving the long-term outlook of dually diagnosed persons.

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Substance Use and HIV Risk Among People With Severe Mental Illness

Francine Cournos and Karen McKinnon

People with severe mental illness are often overlooked in the acquired immunodeficiency syndrome (AIDS) epidemic. For a long time it was assumed that those with schizophrenia, the most common diagnosis in public treatment settings, were too disorganized or withdrawn to engage in the drug use and sexual behaviors related to human immunodeficiency virus (HIV) exposure (Carmen and Brady 1990). The extent of these risk behaviors was unknown and uninvestigated. Unfortunately, this inattention may have facilitated the spread of HIV infection among people with the most severe psychiatric disorders.

This chapter reviews the literature on the role of substance use in HIV risk among people treated in public mental health settings who have recurrent or persistent psychotic illness and significant functional impairments. Most of these people have had multiple psychiatric admissions and courses of psychotropic medications. The majority are unemployed and rely on social welfare benefits. Some are homeless. They typically fit poorly into existing health care and substance abuse treatment programs—they receive inferior medical care, have higher morbidity and mortality, and are unwelcome in traditional treatment programs (Gelberg and Linn 1984; Kroll et al. 1986).

THE EMERGENCE OF THE AIDS EPIDEMIC IN THE PSYCHIATRIC POPULATION

In 1983, a 25-year-old woman hospitalized at a state psychiatric center in Brooklyn, New York developed a low white blood cell count. It was assumed to be caused by the antipsychotic medication she was taking, which was immediately stopped. However, her blood count did not improve. Ten months later she developed pneumonia and was transferred to a general hospital. There was no HIV antibody test at the time, but the organism causing her pneumonia was *pneumocystis carinii*, and a diagnosis of AIDS was made. This woman was one of the first of a series

of patients who would make it clear that AIDS could have a significant impact on the psychiatric population.

This was a shock to psychiatric institutions. Clinicians and hospital administrators of the time thought of AIDS as a disease of men who either had sex with other men or injected drugs. In 1983, there were only 143 newly diagnosed cases of AIDS among women in the entire country, and one of them was at a public psychiatric hospital in New York City. In fact, the majority of early cases reported in the psychiatric literature were women (Cournos et al. 1990; Gewirtz et al. 1988; Horwath et al. 1989). Well into the second decade of the AIDS epidemic, such case reports were the only information in the peer-reviewed literature about HIV infection among psychiatric patients. To what extent these cases were typical or represented an accurate picture of the epidemic in this population was unknown.

THE PREVALENCE OF HIV INFECTION AMONG ADULTS WITH SEVERE MENTAL ILLNESS

The first published study of the prevalence of HIV infection among a psychiatric population appeared in 1991 (Cournos et al. 1991*a*). There are now 11 studies in the peer-reviewed psychiatric literature on the rates of HIV infection among psychiatric patients in treatment in the United States, 10 conducted in New York City and 1 in Baltimore. Rates of infection range from 4.0 to 22.9 percent (Cournos et al. 1991*a*; Empfield et al. 1993; Lee et al. 1992; Meyer et al. 1993; Sacks et al. 1992*a*; Silberstein et al. 1994; Volavka et al. 1991).

One small study conducted outside a hospital setting found that 19.4 percent of mentally ill men attending a day program in a large homeless shelter had a positive antibody test noted in their records (Susser et al. 1993).

Unfortunately, little peer-reviewed research examines seroprevalence among a defined psychiatric population in the United States outside New York City. Anecdotal reports suggest elevated rates of infection in comparison to the general population in other geographic areas (personal communications). Although some psychiatric hospitals have conducted seroprevalence studies without external funding, results have not appeared in scientific journals, possibly because of flawed methods of data collection.

Table 1 summarizes the seroprevalence literature and shows the methodology (anonymous or open), number of subjects, type of psychiatric setting, and percent infected.

TABLE 1. *Methodology, number tested, type of treatment setting, and percent infected in published HIV seroprevalence studies among people with severe mental illness in the United States.*

Study	Method	N	Site	% HIV+
Cournos et al. 1991*a*	Anonymous	451	Public hospital, consecutive admissions	5.5
Volavka et al. 1991	Anonymous and open	515	Public hospital, consecutive admissions	8.9
Sacks et al. 1992*b*	Anonymous	350	Private hospital, new admissions	7.1
Lee et al. 1992	Anonymous	135	Not-for-profit hospital, consecutive admissions	16.3
Empfield et al. 1993	Anonymous	203	Public hospital, homeless psychiatric inpatients	6.4
Meyer et al. 1993	Anonymous	87	Public hospital, homeless psychiatric inpatients	5.8
Susser et al. 1993	Open	62	Homeless shelter, psychiatric service	19.4
Meyer et al. 1993	Anonymous	199	Public hospital, longstay inpatients	4.0
Cournos et al. 1994*b*	Anonymous	971	Public hospital, acute-care, long stay, and homeless inpatients	5.2
Silberstein et al. 1994	Open	118	Public hospital, consecutive dual-diagnosis admissions	22.9
Stewart et al. 1994	Anonymous	533	Public hospital, new outpatient or inpatient admissions	5.8

Methodological Issues in Estimating Prevalence

Estimating how many people with severe mental illness are infected with HIV requires identifying a group to study, learning their demographic and risk characteristics, and obtaining blood samples to test. Differences in the HIV infection rates obtained in seroprevalence studies may be due to differences in sampling and methodology.

Sampling. To map the distribution of HIV and the factors that influence it in the psychiatric population, a representative sample is required. The published seroprevalence studies are all limited by the selection of populations in treatment in hospital settings, who represent only some of those with severe psychiatric disorders. In addition, all were conducted in New York City, where AIDS case rates are higher than in other parts of the United States. In these studies, sampling was carried out over varying timeframes, ranging from 3 (Meyer et al. 1993) to 18 months (Empfield et al. 1993). Changes in rates among subgroups of patients have not been reported and information on the number of new cases (incidence) of HIV infection occurring in the population has not appeared.

Method. Anonymous serosurveys have been described in detail elsewhere (Cournos et al. 1991*a*). Such surveys have several advantages over studies in which patients consent to testing. They capture a larger and more representative proportion of the population under investigation because they sample all patients, not specifically those selected either because they request testing, are urged to have it because of a history of HIV-related risk behaviors, or are capable of giving informed consent. Larger sample sizes increase the statistical power to assess relationships between independent and dependent variables. In addition, infected patients are not individually identified, so there is little direct impact on staff and patients. Anonymous testing does not interfere with clinical judgments about the risks and benefits of testing, and pre- and posttest counseling can be tailored to individual patients. This method is best suited to hospital settings in which large patient pools permit anonymous blood collection.

By comparison, the major advantage of the open testing method, which is contingent on patient capacity to give informed consent, is the possibility of conducting structured diagnostic and risk assessment interviews to obtain detailed and reliable information that can be linked to HIV status. Open testing can be carried out in any setting.

In summary, the number of studies attempting to estimate HIV infection among people with severe mental illness is small. All were conducted in New York City and limited in the type and reliability of information obtained and by the selection of hospitalized people. Nevertheless, they represent the state of the art, and must be used as a basis for further research.

Comparing Rates of HIV Infection Among Psychiatric Patients and Other Groups Studied in New York City

Examining the variations in HIV seroprevalence among psychiatric patients in New York City, it is clear that the lower end of the range of seroprevalence estimates are from research conducted in areas of the city with relatively low AIDS case rates and on psychiatric units that exclude from admission those with primary substance abuse diagnoses. At the high end are studies that have sampled high case rate areas such as the South Bronx and psychiatric units that accept patients with substance use diagnoses.

Rates of infection among psychiatric patients do not simply mirror those among other groups studied in the region. Sampling other populations between 1988 and 1991, the New York City Department of Health found rates of infection of 1.3 percent among women delivering babies, 1.6 percent at abortion clinics, and 1.4 to 2.7 percent at two sentinel hospitals (New York City Department of Health 1990). A study of mentally retarded adults found no HIV-infected individual (Pincus et al. 1990), but among groups considered to be at elevated risk for HIV infection, considerably higher rates were reported. Patients at New York City sexually transmitted disease clinics were found to have an 8.8 percent infection rate in 1990 (Weisfuse et al. 1989).

The relationship between HIV seropositivity and age or ethnicity appears comparable among people with severe mental illness and other groups examined in the epidemic. No clear association between HIV infection and age was found (Empfield et al. 1993; Silberstein et al. 1994), but patients belonging to ethnic minorities had significantly higher rates than caucasians (Cournos et al. 1991*a*, 1994*b*; Silberstein et al. 1994).

One of the distinctive features of the seroprevalence studies among psychiatric patients was that those examining gender differences found that women were as likely as men to be infected. Among men, between 3.8 and 24.0 percent were HIV positive (Cournos et al. 1991*a*; Empfield

et al. 1993; Meyer et al. 1993; Silberstein et al. 1994; Volavka et al. 1991). Rates of HIV infection among women varied from 5.3 to 20.0 percent (Cournos et al. 1991*a*; Empfield et al. 1993; Meyer et al. 1993; Silberstein et al. 1994; Volavka et al. 1991). In the general population in New York City, HIV seroprevalence among men remains markedly higher than among women (New York State Department of Health 1992).

The large proportion of infected women in the psychiatric population reflects a pattern of infection that suggests a link to drug use by injection. Among women with AIDS in New York City, drug injection is a more prominent risk behavior than sex with men at risk (New York State Department of Health 1992).

Rates of HIV infection among people with severe mental illness are relatively low compared to those among injection drug users in New York City, for whom HIV infection has been estimated to range between 29.6 and 44 percent (New York State Department of Health 1992). Nevertheless, the implications of current HIV seroprevalence data for the public mental health system and for patients within that system are very disturbing.

Detection of HIV Infection in Psychiatric Settings

Few psychiatric patients are HIV symptomatic. Comparing anonymous results to infection control records within the same facility reveals that a large proportion are admitted and discharged with their HIV infection undetected (Cournos et al. 1991*a*; Mahler et al. 1994; Sacks et al. 1992*b*). Early in the epidemic there were many disincentives to learning that patients were HIV infected, including housing discrimination and other forms of stigmatization and the stress and anxiety attendant upon learning one is HIV positive. These concerns are now balanced by the important medical and public health benefits of early diagnosis.

In the absence of HIV-related symptoms, detection depends largely on the facility's motivation and resources. On public and private acute admissions units with high physician-to-patient ratios, about one-third of cases went undetected (Cournos et al. 1991*a*; Sacks et al. 1992*b*). The vast majority of cases at a large state hospital and an alcohol rehabilitation unit left undiagnosed (Cournos et al. 1991*a*; Mahler et al. 1994).

Detection of asymptomatic HIV infection is difficult without knowing an individual's risk history. A risk factor is any factor that increases the likelihood of a person developing a disorder. Although people with severe psychiatric disorders have elevated rates of infection, mental illness may not directly increase an individual's chances of acquiring HIV; rather, it appears likely that mental illness mediates the tendency to engage in risk behaviors. Certainly many other factors mediate risk behavior as well.

THE SOCIAL CONTEXT OF HIV INFECTION AMONG THOSE WITH SEVERE MENTAL ILLNESS

Every risk behavior occurs in a context. For people with serious psychiatric disorders, the social conditions under which they live exert influences that are just beginning to be studied systematically.

Severe mental illness can interfere with the normal life tasks of work, intimacy, and the creation of social networks. It is associated with institutionalization, homelessness, and poverty. These factors have been linked to HIV risk-related behavior (Cournos et al. 1991*b*).

THE RELATIONSHIP BETWEEN PSYCHIATRIC ILLNESS AND HIV RISK

How much of HIV risk activity is related to having a psychiatric illness? Little research has adequately addressed this question. One study of outpatients reported that those with personality disorder diagnoses may be at higher risk than those with Axis I syndromes alone (Kalichman et al. 1994). A large study among state psychiatric hospital patients found that women with bipolar disorder were particularly likely to report sex with drug injectors or partners with AIDS (Volavka et al. 1991). However, another study among both inpatients and outpatients showed no association between psychiatric diagnosis and injection drug use or sexual activity (Cournos et al. 1993).

The scarcity of evidence on the connection between specific psychiatric diagnoses or symptoms and HIV risk behavior is a major obstacle to targeted risk assessment. Until more research is conducted using standardized diagnostic and behavioral instruments, people with severe mental illness will continue to be treated as an undifferentiated population

with indistinguishable needs. In the meantime, it is important to track both drug use and sexual risk behaviors in this population because they often co-occur.

The Prevalence of Substance Abuse Among People With Serious Psychiatric Disorders

Many studies of comorbidity show that people with alcohol and drug use disorders have high rates of personality disorder, depression, and, to a lesser extent, anxiety disorders. Whereas only a small number of substance users suffer from severe psychotic disorders, a sizable proportion of people with severe psychotic disorders appear to have comorbid substance abuse disorders.

Comorbid abuse of specific substances and methodological problems in assessing substance abuse in this population have been detailed elsewhere (Galanter et al. 1988; Mueser et al. 1990). Typical limitations are lack of diagnostic rigor, inadequate sample size, and failure to simultaneously assess the multiple substances abused.

Those studies examining the prevalence of any substance abuse disorder since AIDS first appeared show that between 25 and 75 percent of psychiatric patients meet lifetime criteria for alcohol abuse (Drake and Wallach 1989; Safer 1987). The Epidemiologic Catchment Area study found substance use disorders among 47 percent of people with schizophrenia and 61 percent of those with bipolar disorder (Helzer 1988). These high rates of comorbidity put people with severe mental illness at risk for HIV from drug-related behaviors.

Injecting drugs is the most direct drug use risk activity, but there has been very little investigation of this practice among people with severe mental illness. Only recently have a few studies begun to appear. These reveal recent injection among 1 to 8 percent of patients (Hanson et al. 1992; Horwath et al. 1996; Sacks et al. 1990*a*, 1990*b*) and a history of injection among 5 to 20 percent (Cournos et al. 1993; Hanson et al. 1992; Horwath et al. 1996; McDermott et al. 1994; Sacks et al. 1990*a*, 1990*b*). Table 2 shows known injection drug use rates in this population and the timeframes studied.

TABLE 2. *Studies of injection drug use risk behavior among people with severe mental illness.*

Study/State	Method/time frame	N	Site/sample	Prevalence of risk behaviors
Sacks et al. 1990*a*, New York	Survey of therapists re current risk history of patients admitted over 4-mo. period	205	Private acute care psychiatric unit	• Intravenous drug users = 6.3%
Sacks et al. 1990*b*, New York	Consecutive acute admissions; self-report questionnaire of risk for 5 previous years	113	Private acute care psychiatric unit	• Reported IV drug use = 5% • Shared needles or drug paraphernalia = 5%
Hanson et al. 1992, New York	Interview; risk behavior of past year	50	Dually diagnosed adults in hospital-based day treatment	• History of substance abuse: alcohol, cocaine, marijuana were primary drugs; other illicit drugs were used infrequently = 98% • Lifetime opiate abuse = 32% • Reported IV drug use in past year = 8% • Shared needles in past year = 4% • Injected cocaine in past 3 mos. = 2%

TABLE 2. *Studies of injection drug use risk behavior among people with severe mental illness (continued).*

Study/State	Method/time frame	N	Site/sample	Prevalence of risk behaviors
Cournos et al. 1993, New York	Structured face-to-face interview using instrument w/ demonstrated reliability/previous 6 mos.	95	Chronic adult inpatients and outpatients	• Drug injections since 1978: men = 22%; women = 17% • Drug injections past 6 mos. = 1.1%
Kalichman et al. 1994, Wisconsin	Individual structured interviews	97	Outpatients	• Ever injected drugs: men = 6%; women = 2%
McDermott et al. 1994, Los Angeles	Structured interview of sexual risk behavior	61	Public general hospital psychiatric inpatients compared w/ nonpsychiatric controls	• Reported drug injection past 5 years: psychiatric = 15%; control = 3% • Diagnostic groups reporting IDU: Depressive disorder schizophrenia/controls
Horwath et al. 1996, New York	SCID diagnosis and parental drug use interview since 1978	192	Chronic adult inpatients and outpatients	• Lifetime substance abuse or dependence: alcohol = 43% • Cannabis = 33%; cocaine = 26%; any drug = 60% • Reported drug injection since 1978 = 20% • Reported drug injection past 6 mos. = 1% • Drug sniffing as predictor of injection = 32%

Only one interview study (Horwath et al. 1996), conducted in New York City, specifically ascertained drug injection since 1978, the year HIV began to spread in the U.S. population in general (Conant 1984) and among drug injectors in New York City (Novick et al. 1986). These investigators examined the pattern of drug use among inpatients and outpatients at two state-funded psychiatric hospitals, using the Structured Clinical Interview (SCID) for *Diagnostic and Statistical Manual of Mental Disorders*, 3rd. ed. rev. (DSM-III-R) to establish axis I and II diagnoses (Spitzer et al. 1989) and a parenteral drug use questionnaire (Williams et al. 1989).

Because the state hospital system in New York screens out patients believed to have primary alcohol or substance abuse or dependence, only 12 percent of patients met current diagnostic criteria for such a disorder. However, even with such a screen, 60 percent of patients met lifetime criteria for a diagnosis of alcohol or substance abuse or dependence (Horwath et al. 1996).

In addition, 20 percent of patients had injected drugs since 1978 (Cournos et al. 1993; Horwath et al. 1996). This was an unanticipated finding. Because so few people with mental illness are currently injecting, the extent of the previous history of this behavior has been overlooked. However, 70 percent of people who previously injected may resume this practice (van Ameijden et al. 1994).

Although the literature reveals virtually nothing about when, why, and under what circumstances this population injects drugs, one noteworthy report indicates that 32 percent of psychiatric inpatients and outpatients reported intranasal drug use, and the likelihood of also being an injector increased fourfold among those reporting this behavior compared to those who do not (Horwath et al. 1996).

The importance of drug injection in the transmission of HIV infection is illustrated by a small study of 42 known HIV-positive people hospitalized in a state psychiatric center in New York City. Here, injection drug use emerges as a very prominent risk behavior. Seventy-one percent of men and 56 percent of women had engaged in this practice (Meyer et al. 1995).

The relative contributions of injection drug use and sexual activity to HIV infection in this population are not yet known. One study that ascertained risk behaviors from patients' charts found that injection drug use and homosexual activity contributed about equally to the risk of HIV among

mentally ill men. In addition, injection drug use was the most powerful vector of transmission for women with serious psychiatric illnesses (Cournos et al. 1991*a*).

The Interaction of Substance Use and Sexual Risk Behaviors in the Psychiatric Population

For a long time, many clinicians assumed that people with severe mental illness were sexually inactive. There was little reason to think otherwise, since mental health professionals tended to believe that talking to psychotic people about sex would be distressing. They were right. It was distressing—but to the staff rather than the patients. In fact, psychiatric patients report enjoying talking about sex. In one interview study, patients reported feeling relieved not to have to talk about their psychiatric symptoms all the time and to be asked about a normal aspect of life (McKinnon et al. 1993). These researchers found that when staff are able to overcome their anxieties, the majority of patients are able to comfortably give reliable sexual histories.

A dozen studies have appeared that examine sexual risk behavior in the psychiatric population (Cournos et al. 1991*b*, 1994*a*; Hanson et al. 1992; Kelly et al. 1992; McDermott et al. 1994; Sacks et al. 1990*a*, 1990*b*; Stevenson et al. 1993). Across these, at least half of the patients who were asked about recent sexual activity with a partner, which occurred during the past 6 to 12 months, reported being active (Cournos et al. 1993, 1994*a*; Hanson et al. 1992; Kalichman et al. 1994; Kelly et al. 1992; McDermott et al. 1994; Stevenson et al. 1993). Although this demonstrates that a significant proportion of people have a recent history of abstinence, those not currently sexually active may nevertheless have engaged in sexual risk behaviors in the past.

Those patients who do report recent sexual activity have engaged in multiple risk behaviors. Between 19 and 62 percent of the people who were sexually active had had more than one partner in the past 6 to 12 months (Cournos et al. 1993, 1994*a*; Hanson et al. 1992; Kelly et al. 1992; Kalichman et al. 1994; Sacks et al. 1990*a*). The majority of sexual episodes involved heterosexual vaginal or anal intercourse.

When asked about their sexual orientation, the men who were interviewed in these studies almost all identified themselves as heterosexual (Cournos et al. 1993, 1994*a*; Kelly et al. 1992). Yet, 2 to 10 percent had had recent

homosexual activity (Cournos et al. 1993, 1994*a*; Kelly et al. 1992; Stevenson et al. 1993; Susser and Valencia 1993), and about 1 in 5 reported lifetime homosexual behavior (Cournos et al. 1993, 1994*a*). This suggests that a substantial minority of mentally ill men engage in this behavior intermittently and that an accurate risk history cannot be obtained by asking patients about their sexual orientation. In addition, high rates of intermittent homosexual behavior among men may occur at times when they are living in all-male settings such as psychiatric wards, shelters, or prisons where condoms are typically not available on demand.

One confirmation of the importance of homosexual activity as a prominent vector for HIV transmission among psychiatric patients is a small study of 24 men hospitalized at a state psychiatric center who were known to be HIV infected. Of these, 42 percent had a history of homosexual activity (Meyer et al., in press).

Overall, condom use during intercourse is infrequent. Only 8 to 25 percent of patients surveyed reported using condoms consistently (Cournos et al. 1993, 1994*a*; Susser and Valencia 1993). Between 12 and 39 percent of sexual episodes were protected (Cournos et al. 1993).

In general, there is a well-known association between unsafe sexual activity and alcohol or drug use. Only a few studies have examined the co-occurrence of these behaviors among people with severe psychiatric disorders. These studies are summarized in table 3.

Patients with both psychiatric and substance abuse diagnoses have sexual contacts with other drug users (Hanson et al. 1992). Even patients without a comorbid alcohol or drug abuse disorder have sexual partners who are actively using drugs, including injected drugs. Between 8 and 12 percent of patients report sex with a partner who is an injection drug user (Cournos et al. 1994*a*; Kalichman et al. 1994).

Trading sex may occur because most people with severe mental illness are indigent. If they are in an institutional setting, they have minimal spending money. If they are living in the community, they usually receive entitlement benefits that keep them well below the Federal definition of poverty. Sex is a commodity that can be exchanged for money, drugs, a place to stay, and cigarettes. Research shows that between 12 and 69 percent of psychiatric inpatients and outpatients with recent sexual activity report exchanging sex in this manner (Cournos et

TABLE 3. *Studies of co-occurring sexual and drug use risk behavior among people with severe mental illness.*

Study/State	Method	Total N	Sexually active N	Site/sample	Prevalence of risk behaviors
Cournos et al. 1991*b*, New York	Structured face-to-face interview for sexual and drug use behaviors; previous 6 mos.	160	88	Adult inpatients and outpatients	• Frequent drug use during sex: alcohol, marijuana, crack/cocaine • Frequent sex trading for drugs, food, rent, cigarettes, money
Hanson et al. 1992, New York	Interview; risk behavior of past year	50	"most"	Dually diagnosed adults in hospital-based day treatment	• Traded sex for drugs = 12% • Sex w/ drug users = 28%
Susser and Valencia 1993, New York	Standardized interviews on sexual and drug use risk	89	44 (28 w/ women only; 6 w/ men only; 10 w/ both)	Homeless shelter for men	• Received from men, drugs or money for sex = 69% • Gave to women drugs or money for sex = 47%
Cournos et al. 1994*a*, New York	SCID diagnosis and structured face-to-face interview for sexual behaviors using instrument w/ demonstrated reliability; previous 6 mos.	95	42	Adult inpatients and outpatients w/ diagnosis of schizophrenia	• Drug use during sex = 45% • Sex exchange = 50% • Sex w/ drug-injecting partner = 12%
Kalichman et al. 1994, Wisconsin	Structured interview	61	51 in past year	Psychiatric outpatients	• Sex w/ IVDU ever: men = 8%; women = 9% • Used drugs or alcohol before sex = 36% • Received money or drugs for sex = 18%

al. 1991*b*, 1994*a,b*; Hanson et al. 1992; Susser and Valencia 1993; Kalichman et al. 1994).

Consistent with this practice are the findings of two studies conducted in the Midwest that examine the details of recent sexual encounters among mentally ill outpatients. Prevalent behaviors included sex with unfamiliar or transient partners, often met in bars, clinics, or on the street, and sometimes involving coercion (Kalichman et al. 1994; Kelly et al. 1992). Although these findings are suggestive, the interaction between unsafe sex and drug use has not been specifically investigated among people with severe mental illness.

RESEARCH NEEDS

It is difficult to know whether people with severe mental illness engage in more types of HIV risk behaviors or do so more frequently than others. Very few data exist on the prevalence of these behaviors in the general population. A recent study on sex in America (Gagnon et al. 1994) showed that most people choose sexual partners who resemble them in race, religion, age, socioeconomic level, and education so that once AIDS enters a population, it tends to remain concentrated there. This finding is relevant to psychiatric inpatients and outpatients because HIV is already prevalent among them.

The cumulative evidence from the literature on HIV risk in this population indicates that a large proportion of people with recurrent or persistent psychotic illness will at some point meet criteria for alcohol or drug abuse or dependence. Risk of HIV infection increases both by unsafe sexual activity and drug injection. It is not yet clear to what extent noninjectable drug use contributes to HIV risk through sexual disinhibition or sex trading. Much more research in this area must be undertaken to understand the impact on HIV risk of substance use and abuse or dependence on those with psychotic illness.

AIDS is a preventable disease. In fact, psychiatric inpatients and outpatients are quite knowledgeable about AIDS, and are capable of learning the facts about how HIV is spread and the importance of prevention efforts (Herman et al. 1994). Prevention efforts must simultaneously address primary psychiatric disorders, sexual risk behaviors, drug use risk behaviors, and the difficult social conditions patients must deal with. Taking appropriate risk behavior histories from

people in treatment is an important first step in preventing the spread of HIV among psychiatric patients. These histories must include an assessment not only of recent but also of past behaviors associated with increased risk of HIV exposure.

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Depression, Substance Use, and Sexual Orientation as Cofactors in HIV-1 Infected Men: Cross-Cultural Comparisons

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INTRODUCTION

The co-occurrence of major depression in medical populations has been the subject of much controversy in the past decade. Although some investigators have suggested that reports of an increased prevalence of depression may, in part, be due to misclassification based on physician reliance on self-report methods (Perez-Stable et al. 1990) or on failure to adjust for symptoms induced by physical illness (Plumb and Holland 1977), most studies have suggested that the prevalence of depression is high, although often undetected by the primary care physician (Perez-Stable et al. 1990; Schulberg et al. 1985). Schulberg and colleagues (1985) state that it is unclear whether this oversight reflects true limitations in the physician's diagnostic acumen, his/her lack of concern for social implications, or whether it is an artifact of existing classification procedures. Regardless of the reasons for its underreporting, the detection and treatment of depression is crucial, especially for medically ill patients, because depressive disorders may adversely affect survival, length of hospital stay, compliance with therapy, ability to care for oneself, and quality of life (Schulberg et al. 1985).

These concerns are particularly relevant to human immunodeficiency virus type 1 (HIV-1), where the co-occurrence of major depression has received only limited recent attention. Based on initial reports using chart reviews (Perry and Tross 1984), it has been suggested that over 83 percent of hospitalized acquired immunodeficiency syndrome (AIDS) patients have significant disturbances in mood. Unfortunately, anecdotal studies such as this fail to use structured diagnostic interviews to distinguish transitory dysphoria in response to the clinical condition and its treatment from syndromal depression. The latter disorder is more serious and merits direct clinical intervention because it may be predictive

of more accelerated course and early mortality. In addition, such reporters do not investigate other cofactors that could account for the co-occurrence of depression in HIV-1 disease.

The purpose of this chapter, therefore, is to examine the evidence of the co-occurrence of major depression in persons infected with HIV-1, with special attention to the potential role that cofactors such as substance use and sexual orientation (i.e., being gay or bisexual) might play in accounting for the association. The chapter is organized into two parts. Part I presents a brief summary of the literature on syndromal depression in HIV-1 that was part of a larger review on the assessment of mood disorder in medical populations (Satz et al., in press). Part II presents a reanalysis of data from two large recent cohort studies of HIV-1 in populations in the United States and abroad, the World Health Organization (WHO) Multicentre Study of HIV-1 (Maj et al. 1994*a*, 1994*b*). The latter provides a more direct test of the relationship of syndromal depression in HIV-1, with special focus on substance use and sexual orientation as important cofactors.

PART I

Syndromal Depression and HIV-1 (Summary Review)

There are eight studies in the literature that report the prevalence of current and/or lifetime major depression in HIV-infected adults. Each study used structured diagnostic interview instruments and *Diagnostic and Statistical Manual of Mental Disorders*, 3d ed. revised (DSM-III-R), or ICD-10 criteria to define syndromal disorder. The results from these studies, which are summarized in table 1, indicate two general findings. The first is that none of the studies found an association of HIV-1 with lifetime depression, and only one found an association with current (1 month) depression (Baldeweg et al. 1993). In addition, none of the studies reported an association between either lifetime or current depression and early (presymptomatic) HIV-1 infection.

The second finding is that, despite the general lack of association between major depressive disorders (MDD) and HIV-1, the rates for both current and lifetime depression in HIV-infected persons were significantly higher than the prevalence rates for depression in the general population reported in both the Epidemiologic Catchment Area (ECA) study (Regier et al. 1988) and in the more recent National Comorbidity Survey (NCS)

(Kessler et al. 1994). The average prevalence rates for lifetime MDD in HIV seropositive men (23.7 percent) was approximately fivefold higher than the average rate reported for men in the ECA (4.6 percent) and 1.8 times higher than reported for men in the NCS (13 percent). With respect to current depression, the observed rates were approximately 3.8 times higher than reported for 1-month ECA rates for men (2.3 percent). NCS rates for current major depression were available only for the past 12 months. Comparisons are presented for men only because the studies of HIV-1 included primarily well-educated, white, gay, male volunteers, which reflects the population most affected in the first wave of the disease. For example, in five of the studies the participants were described as gay or bisexual (Tross et al. 1987; Atkinson et al. 1988; Williams et al. 1991; Baldeweg et al. 1993; Perkins et al., in press). Given the population trends for this disease, it is very likely that the majority of the participants in these early studies were gay or bisexual.

Despite the generally null findings regarding the association between MDD and HIV-1, one must note that few studies contrasted the spectrum of HIV-1 infection (Tross et al. 1987; Atkinson et al. 1988; Baldeweg 1993), while other studies pooled cases of presymptomatic and symptomatic HIV-1 infection (Perry 1990; Pace et al. 1990). The pooling of early stage and advanced stage patients could attenuate the HIV-MDD association if the latter is more likely to be present in advanced cases. Also, most studies had small sample sizes, which restricts power to detect an association between these putative comorbid outcomes.

The consistently high rates of MDD across studies, regardless of serostatus, raises the question of whether sexual orientation or other factors may be unexamined independent risk factors for major depression. Only one study (Atkinson et al. 1988) explored this hypothesis by including two small samples of noninfected gay (N = 11) and heterosexual (N = 22) controls. This study was the first to show an elevated rate of MDD in the gay and bisexual groups, independent of serostatus, suggesting that sexual orientation and lifestyle may be risk factors for major depression.

It is also noteworthy that despite evidence of significant substance abuse among those at highest risk for HIV-1 infection (Donahoe 1990; Parker and Carballo 1992), none of these studies investigated whether the increased prevalence of depression in their samples may have been attributable, either directly or indirectly, to the widespread abuse of alcohol and other substances.

TABLE 1. *Prevalence (%) major depressive disorder (MDD) for current (past month) and lifetime by studies versus ECA rates.*

Study	HIV-1 status	N	Sex. orient.	Percent Current	ECA	Percent Life	ECA	Comments
Tross	SN	149		4.7				
et al. 1987	ARC	40	G/B	15.0	2.2			No HIV effect
	AIDS	90		13.0				High % MDD
Atkinson	CONT	22	HET	0.0[1]		9.1		No HIV effect
et al. 1988	SN	11		9.1		36.4		High % MDD
	ASP	17	G/B	17.6		35.3		in G/B
	ARC	13		7.7		38.5		
	AIDS	15		6.7		13.3		
Perry1990	SN	103	Mixed	4.9		30.1		No HIV effect
	ASP	51		3.9	2.2	25.5	4.4	High % MDD Females higher % MDD
Pace	ASP	95	Mixed	5.8	2.8	5.3	7.0	No HIV test
et al. 1990								No increase MDD
Williams	SN	84		4.0		33.0		No HIV effect
et al. 1991	HIV+	124	G/B	4.0	2.2	32.0	3.0	High % MDD
Brown	HIV+	442	Mixed	6.3	2.0	22.4	7.8	No HIV test
1992								High % MDD
Perkins	SN	71		3.0		32.0		No HIV effect
et al., in	ASP	98	G/B	8.0	2.2	28.0	3.1	High % MDD
press								
Baldeweg	SN	38		8.0[2]				HIV effect
et al. 1993	ASP	59		3.0				(current)
	SSP	48	G/B	31.0				High % MDD

KEY: 1 = Heterosexual control; 2 = currrent equals 6 months.

In summary, these studies suggest that there does not appear to be a consistent association between HIV-1 serostatus and major depression, although groups at highest risk for this disease also appear to be at high concurrent risk for major depression. However, a more definitive test of the question of whether HIV-1 disease is associated with increased risk for depression will require larger study samples with adequate representation across the HIV-1 spectrum, including heterosexuals, gays, and bisexuals, to determine the independent and interactive effects of HIV disease and sexual orientation on major depression. Also, because most studies employed predominately well-educated, gay or bisexual, white male volunteers, results cannot be generalized to populations in developing countries, which now account for 85 percent of HIV-1 infection in the world and where primary transmission is through heterosexual intercourse (WHO 1992; Maj et al. 1994*a*). The results also cannot be generalized to ethnic minorities in the United States, especially to African Americans and Hispanic Americans, who constitute the groups at highest risk for infection in the second wave of the disease (Peterson and Marin 1988; Krueger at al. 1995). Finally, it is also possible that the widespread abuse of alcohol and other recreational drugs may enhance risk for both HIV-1 infection and major depression in high-risk groups (e.g., gays and bisexuals, intravenous (IV) drug users, and cocaine abusers).

The next section reviews and reanalyzes data from two large cohort studies of HIV-infected men that afford an opportunity to investigate the hypothesized role of sexual orientation and substance abuse as cofactors in the increased prevalence of MDD in HIV-infected men.

PART II

Cross-Cultural Comparisons: The WHO and AAHP Studies

The WHO Multicentre Study of HIV-1 Infection. The WHO project investigated the relationship of neuropsychological, neurological, and psychiatric correlates of HIV-1 infection in a large, representative sample of adults in the five geographic areas predominately affected by the HIV-1 epidemic: sub-Saharan Africa (Nairobi, Kinshasa), South America (Sao Paulo), Western Europe (Munich), and Southeast Asia (Bangkok). The two African sites were selected because they accounted for approximately 60 percent of the world's cases of HIV-1 during the late 1980s (WHO 1990). The additional sites were also selected to represent geographic areas disproportionately affected by the epidemic

and that provided appropriate medical resources and access to outpatient recruitment. A total of 955 subjects (203 in Nairobi, 205 in Kinshasa, 178 in Sao Paulo, 183 in Munich, and 186 in Bangkok) were recruited for the cross-sectional phase. Subjects were predominantly male (704/955 = 73.7 percent) and self-reported heterosexual (798/955 = 83.6 percent) across sites. Results of the pilot phase, including a description of the study, were reported by Maj and colleagues (1991). Results of the cross-sectional phase were reported separately for the psychiatric (Maj et al. 1994*a)* and for the neuropsychological and neurological findings (Maj et al. 1994*b*).

For purposes of this review, only the psychiatric results are presented and discussed. Psychiatric assessments in the WHO study were based on three measures: (1) the Composite International Diagnostic Interview (CIDI) (WHO 1987), which is a structured interview that yields ICD-10 (WHO 1992) and DSM-II-R diagnoses; (2) the 18-item version of the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962); and (3) the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979). Because of possible linguistic and cultural differences between the samples, special care was taken to ensure the reliability and validity of these assessments.

Maj and colleagues (1994*a*) reported the results for each of the major psychiatric disorders for each study site. However, the present technical review discusses only results specific to syndromal major depression, both in terms of overall prevalence and of its association with HIV serostatus, sexual orientation, and substance use. Results for syndromal depression indicated that there was no association with HIV-1 and lifetime depression at any of the sites, and only one of the sites (Bangkok) showed an association between HIV seropositivity and current (past month) major depression. The results from the five study sites, when compared with the findings from the preceding eight studies, indicate no association between HIV-1 and lifetime occurrence in any of the studies, and only two studies reported association with current (past month) occurrence (Baldeweg et al. 1993; Maj et al. 1994*a*, Bangkok site). Comparisons of the prevalence rates for current and lifetime MDD in each WHO site and in other population surveys are in a later section of this chapter.

It is especially noteworthy that there is little support for the expected association of HIV-1 and major depressive disorder, even in individuals with great cultural, ethnic, and educational diversity. However, it is possible that the null findings may be attributable to small samples at

each site (an average of 191 subjects/site) or to the confounding of other risk or comorbid factors (i.e., sexual orientation, substance abuse). As noted previously, only one study (Atkinson et al. 1988) directly investigated the effects of sexual orientation on major depression and HIV-1, and no published study has investigated the effects of substance abuse on this association.

In testing the alternative hypotheses using the WHO data, subjects were pooled across sites (N = 955) to increase statistical power in testing the association between HIV-1 and current major depression (regardless of sexual orientation or substance abuse). In contrast to prior WHO findings (Maj et al. 1994*a*), the pooled results reveal a significantly greater prevalence of current major depression as a function of HIV-1 disease stage ($\chi_2 = 8.5$, $p < 0.01$). In fact, there was almost a fivefold greater prevalence of current depression in the seronegative group (SN = 1.9 percent) when compared to the symptomatic seropositive group (SSP = 9.9 percent) (see figure 1).

There was also a significant association between HIV-1 status and lifetime major depression, indicating almost a threefold greater prevalence of major depression in the SSP group than in the SN group (23.5 percent versus 9.4 percent, $\chi_2 = 6.2$, $p < 0.01$) (see figure 2). These pooled results differ from the original report (Maj et al. 1994*b*), which found no association when results were analyzed separately for each site. However, this difference may reflect, in part, the effects of increased sample size and power. For example, the difference between symptomatic seropositives and seronegatives for lifetime major depression was of the same magnitude in two of the WHO sites as in the pooled sample.

These results raise the additional question of whether the differences may be explained by the confounding of serostatus with other risk factors such as sexual orientation and comorbidity for substance abuse. The following analyses address this hypothesis, providing a reasonable but not ideal test because of the sample composition on the cofactors across four of the sites. For example, the two African samples (Nairobi and Kinshasa) included exclusively heterosexual and predominately non-intravenous drug users (non-IDU) (98 percent) participants. The Bangkok sample also included primarily heterosexuals (93 percent), but a significant majority were IDUs (74 percent). In contrast, the Sao Paulo sample included a majority of gays and bisexuals (51 percent) and non-IDUs (89 percent). The Munich sample was more heterogeneous with respect to these cofactors and was, therefore, dropped from the subsequent analyses.

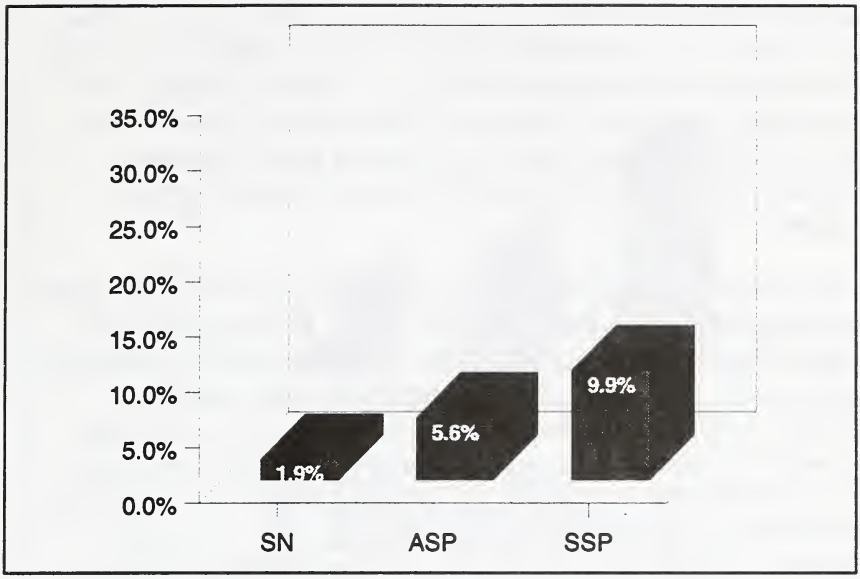

FIGURE 1. *Prevalence of major depressive episode (past 30 days) by serostatus among subjects in the WHO Multicentre Study (N = 955).*

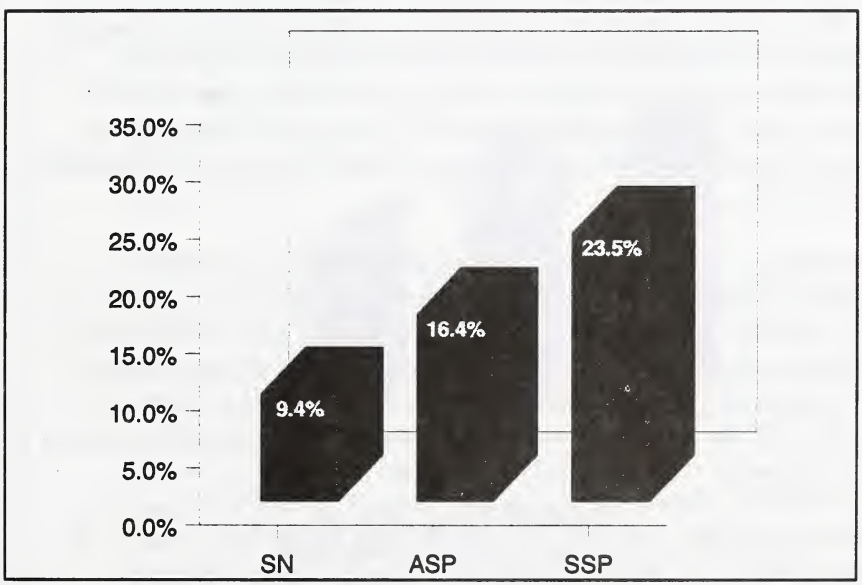

FIGURE 2. *Prevalence of major depression (lifetime) by serostatus among subjects in the WHO Multicentre Study (N = 955).*

The effects of the preliminary risk groupings and HIV status on current major depression are presented in figure 3. What is striking is the strong association of sexual orientation (being gay or bisexual) and IDU with current major depression. In fact, when these risk factors are excluded and one looks only at the non-IDU heterosexual group (Nairobi, Kinshasa), the association between HIV status and major depression disappears.

Similar and more robust effects of sexual orientation and IDU for lifetime major depression can be seen in figure 4. Again, excluding these risk groups eliminates the association between HIV status and major depression among the non-IDU heterosexuals. If replicable, these results are instructive with respect to the putative association between HIV status and major depression. If potential confounders, including comorbidity, are not controlled for, it is possible to reach quite different and misleading conclusions regarding a controversial hypothesis. However, caution should be used against overinterpreting even these findings because of the differences in sexual orientation and substance abuse across the WHO sites. The tests of sexual orientation and substance abuse noted above may be misleading due to the confounding of sexual orientation and ethnocultural origins. As noted in figure 3, the heterosexual/non-IDUs are all Africans, the heterosexual/IDUs are mainly Thais, and the gay/bisexual/IDUs are mainly Brazilians. It is possible that the observed effects could be attributed to unexamined sociocultural differences associated with sexual orientation, drug use, and major depression in these societies. Also, gay/bisexual/non-IDUs were not represented in these comparisons, which limits the test of sexual orientation independent of IDU status.

To partially control for some of these problems, a stepwise logistic regression analysis was conducted on the total sample pooled across the five study sites (N = 955) for current (1 month) and lifetime depression with drug use, sexual orientation, education, age, and serostatus entered as independent variables. Consistent with the first set of analyses of pooled data, the results showed that HIV status was the major predictor of both current ($\chi^2 = 8.2$, $p < 0.01$) and lifetime depression ($\chi^2 = 18.8$, $p < 0.00001$). However, drug abuse ($\chi^2 = 4.3.2$, $p < 0.05$) and gay or bisexual orientation ($\chi^2 = 4.1.2$, $p < 0.05$) were significant predictors of lifetime depression only in symptomatic seropositives compared to seronegatives. This suggests that serostatus is the best predictor of both current and lifetime major depression across the HIV spectrum, when

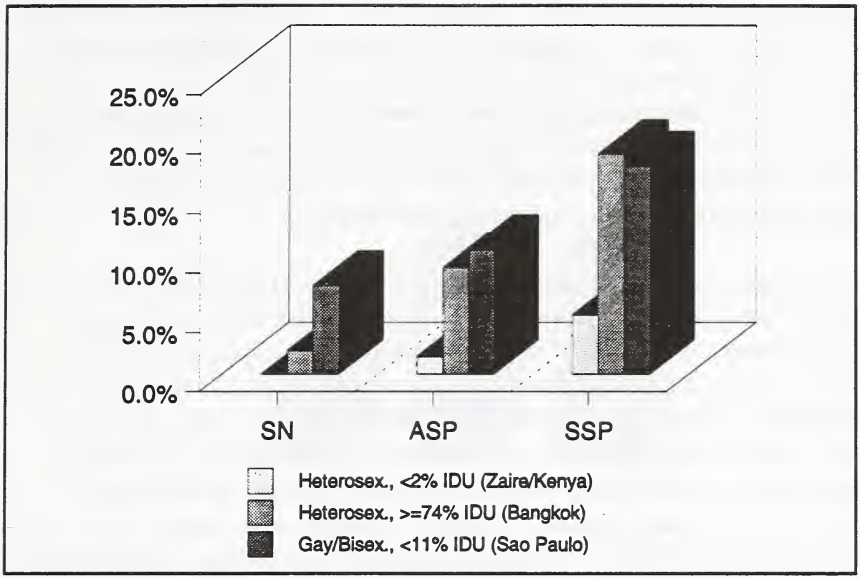

FIGURE 3. *Prevalence of current major depressive episode by serostatus and cofactors among subjects in the WHO Multicentre Study.*

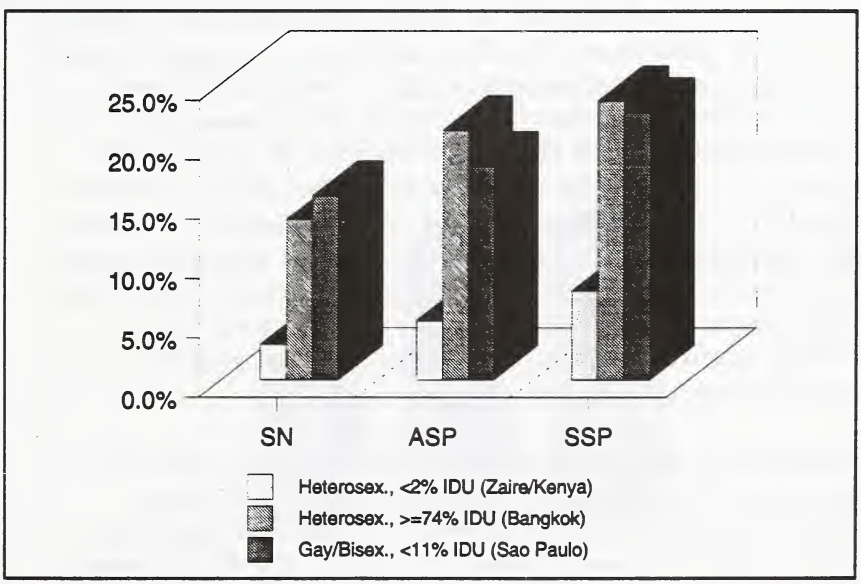

FIGURE 4. *Prevalence of lifetime depression by serostatus and cofactors among subjects in the WHO Multicentre Study.*

sexual orientation and substance abuse status are controlled for. The two latter cofactors, however, appear to be important in predicting enhanced risk for depression only in those with full-blown AIDS. Because of the noted caveats about the unbalanced representation of sexual orientation in the sample and the limited assessment of substance use, the findings need to be replicated before firm conclusions about the association among these predictors and major depression can be drawn.

The African-American Health Project (AAHP). The AAHP was designed to investigate the neurobehavioral sequelae of HIV infection and substance use in urban African-American men (Myers et al. 1994). The study used a cross-sectional design on a sample of 502 African-American men from Los Angeles who differed by serostatus, drug use status, and sexual orientation. Los Angeles was initially considered as a sixth study site of the WHO Multicentre Study and included the same psychiatric assessment protocol, along with several new assessment domains (psychosocial, neuroimaging, neurological, sexual orientation, and drug usage) and an expanded neuropsychological assessment battery. The AAHP study design and assessment features afford an opportunity to investigate more thoroughly the hypothesized relationship between HIV serostatus and major depression, while controlling for sexual orientation and substance abuse.

Sexual orientation and drug use were assessed by detailed interviews and questionnaires administered to all study participants. Approximately half of the cohort was heterosexual and half gay or bisexual. However, almost all of the heterosexuals (94 percent) were HIV seronegative (N = 233), whereas most of the gays and bisexuals (69 percent) were seropositive (N = 172). These demographics reflect, in part, the major risk for HIV-1 transmission in adult men, including African Americans, which is predominately male-male sexual contact. In fact, heterosexual transmission accounts for less than 2 percent of current AIDS cases (Los Angeles County Department of Health Services). A more detailed description of this study's design and overall preliminary results was reported recently by Myers and colleagues (1994).

The results of the analyses on the association between HIV status and current (past 12 months) major depression, unadjusted for sexual orientation or substance use, are presented in figure 5. A significantly greater prevalence of major depression was found in the two seropositive groups than in the seronegative group (20 versus 8.7 percent ($\chi^2 = 19.7$, $p < 0.003$).

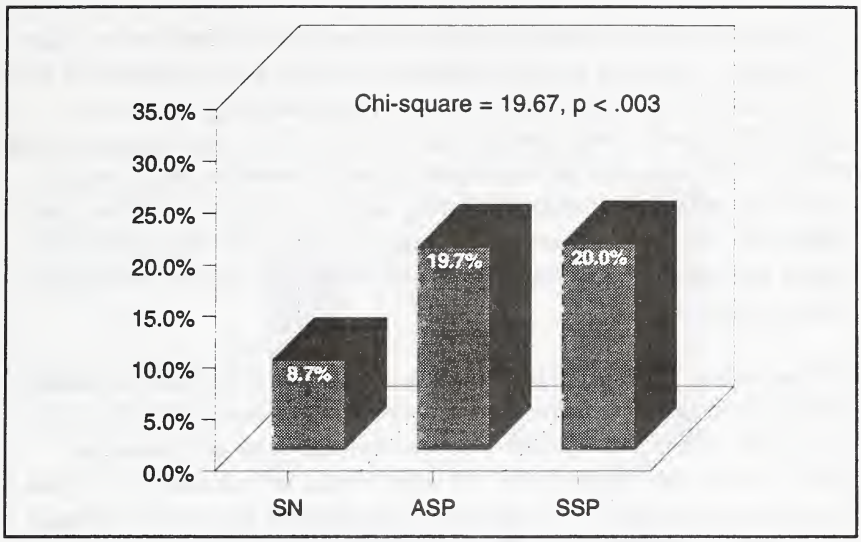

FIGURE 5. *Prevalence of major depression (past 12 months) by serostatus among subjects in the AAHP (N = 502).*

The results for lifetime major depression are presented in figure 6. Again, there is a twofold greater prevalence of major lifetime depression in the two seropositive groups (27.6 percent and 29.1 percent) versus the seronegatives (14.1 percent ($\chi^2 = 21.1$, $p < 0.002$)).

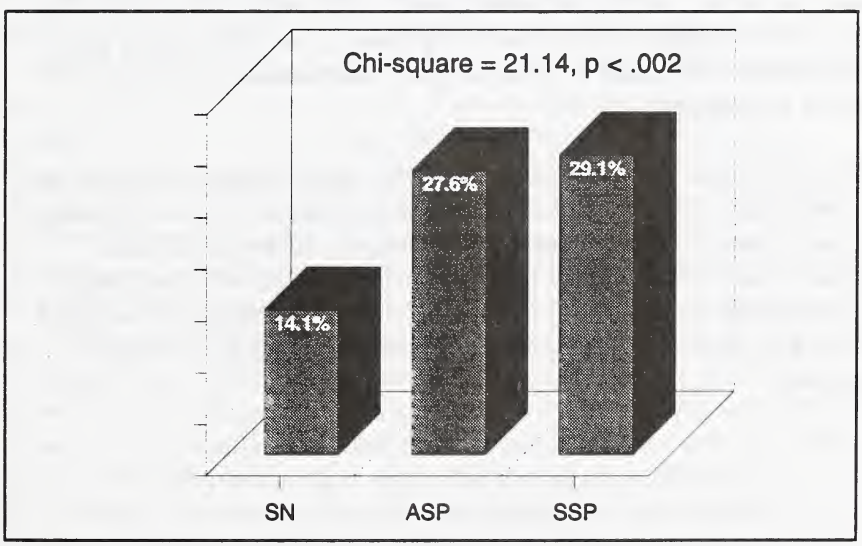

FIGURE 6. *Prevalence of major depression (lifetime) by serostatus among subjects in the AAHP (N = 502).*

To determine whether this association was partly accounted for by other risk factors, a stepwise logistic regression analysis was computed for both current and lifetime depression using a forward-stepping maximum-likelihood method. Demographic characteristics (i.e., age, education, and income), serostatus, sexual orientation, sexual orientation by serostatus interaction term, four indicators of drug use (i.e., years of drug use, past regular use, current drug use of six drugs by urine toxicology, and IDU status), and number of standard drinks of alcohol per week were entered in the analysis.

The results indicate that the best predictors of both recent (past 12 months) and lifetime depression in this sample were sexual orientation (OR = 3.36 and 2.25 for recent and lifetime, respectively) and years of cocaine use (OR 1.05 and 1.04, respectively). In other words, in both analyses, sexual orientation and duration of cocaine use accounted for most of the variance in the prevalence of recent and lifetime major depression, and were more important than serostatus.

It should be remembered, however, that sexual orientation and seropositivity were partially confounded in this sample due to the overrepresentation of gays and bisexuals among the seropositives. Therefore, this test of the relative contribution of serostatus is limited. However, as noted in figure 7, the effect of sexual orientation on major depression was quite robust, even when serostatus was controlled by comparing the prevalence of lifetime major depression among the seronegatives. The results indicate that there was a twofold greater prevalence of depression in the seronegative gays and bisexuals compared to the seronegative heterosexuals (22 percent versus 11 percent).

The results from the reanalyses of the WHO data and the AAHP data are contradictory: The WHO data indicate that serostatus is the best predictor of major depression, both current and lifetime, and the AAHP data indicate that sexual orientation and cocaine use are the better predictors. The questions of what accounts for these divergent findings are explored in the next section by considering differences between the two study samples.

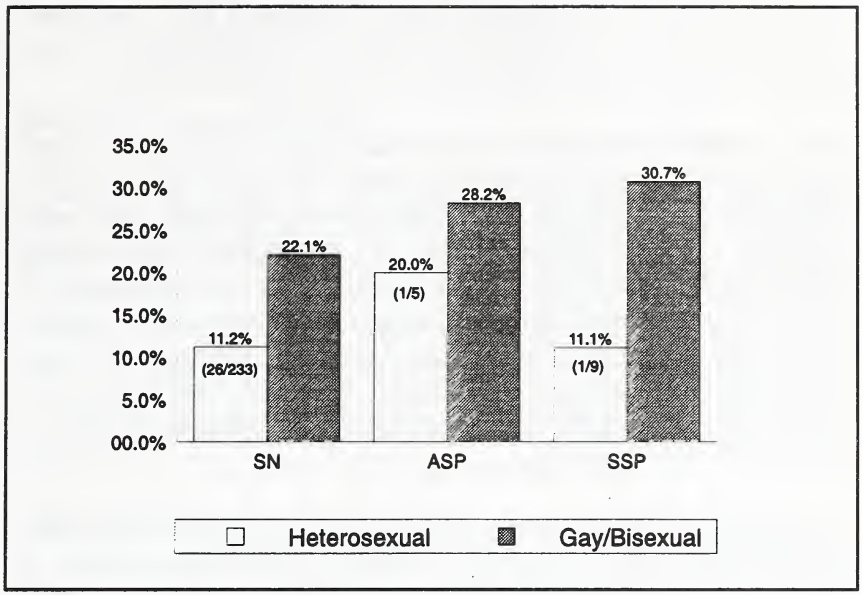

FIGURE 7. *Prevalence of lifetime major depression by serostatus and sexual orientation among subjects in the AAHP.*

Comparisons Between the WHO and AAHP Studies. There are striking differences in the rates of both current and lifetime major depression (both overall and as a function of HIV disease stage) in the WHO and AAHP samples, with the rates in the AAHP significantly higher (see figures 1 and 2 versus 5 and 6). Thus, for example, an average 5.8 percent (current) and 16.4 percent (lifetime) of the WHO sample met criteria for major depression, compared to 16 percent (current) and 23.6 percent (lifetime) of the AAHP participants. However, uncritical evaluation of these differences is misleading. For example, part of the threefold difference in the rate for current depression between the WHO and the AAHP is probably due to differences in the time referent (i.e., 30 days in the WHO and 12 months in the AAHP). A direct comparison of these rates is inappropriate. However, comparisons of lifetime rates are more appropriate, and they indicate that the discrepancy between the WHO and AAHP is most striking among the asymptomatic seropositives (16.4 versus 27.6 percent, respectively) and smallest among the seronegatives (9.4 versus 14.1 percent, respectively). Possible factors that may account for this apparent differential vulnerability include the fact that the seropositives in the AAHP were primarily gays or bisexuals who, as noted previously,

appear to be at greater risk for depression independent of HIV-1 serostatus. These results are also consistent with the high rates of depression, regardless of HIV-1 status, noted in part I of this chapter (see table 1).

Factors in addition to sexual orientation that might be implicated include the psychological costs of racial conflict and relative socioeconomic deprivation in the context of a more affluent society, the stigma associated with HIV-1 as a disease transmitted primarily through homosexual contact, and possible differences in the degree of tolerance of homosexuality in African-American communities compared to other communities in the United States and abroad. In any event, these data suggest greater vulnerability to depression, at least lifetime, in the U.S. sample of African-American men than in the multiethnic/multinational samples studied in the WHO project.

Comparisons of the WHO and AAHP Studies Versus Community Surveys in the U.S. Some additional insights into the relationship between HIV-1 and major depression are afforded by comparing disorder rates in the two studies with those obtained in larger community epidemiologic surveys in which HIV-1 status was not a selection criterion. Such surveys provide a referent base rate for the prevalence of major depression in the population that is relatively independent of HIV-1. Two such surveys of the U.S. population are available for comparison, the ECA (Regier et al. 1988; Robins et al. 1984) and the more recent NCS (Kessler et al. 1994). Unfortunately, similar epidemiologic surveys in developing countries that would be a more appropriate reference for the WHO study are not available.

It was decided to use data from NCS rather than the ECA as the relevant sample for both cohorts for the following reasons: (1) In contrast to the ECA, the NCS was based on a stratified, multistage area probability sample of persons aged 15 to 54 years in the noninstitutionalized civilian population of the 48 contiguous States; (2) the NCS capture a lower and more representative age span than the ECA, which may contribute to higher rates of current and lifetime depression; (3) the NCS diagnoses using the structured CIDI are based on DSM-III-R rather than the DSM-III criteria used in the ECA; (4) the CIDI is also a more sensitive instrument and uses more detailed probes for depression than the ECA Diagnostic Interview Schedule (DIS) (Blazer et al. 1994), which tends to underdiagnose cases of major depression (Schulberg et al. 1985); and (5) the NCS interview contains a more comprehensive risk factor battery

(including family psychiatric history using research diagnostic criteria) than the ECA interview.

The WHO Versus the NCS

Comparison rates for current and lifetime depression for the WHO and the NCS are presented in table 2. The table shows prevalence rates for the total WHO sample of seronegatives (pooled across sexual orientation and drug status) as well as for the seronegatives in the two African sites (Kinshasa and Nairobi), which were comprised almost exclusively of non-IDU heterosexuals (men and women). As noted earlier, the WHO rates of current depression (past 30 days) are likely to be lower than the NCS rates (12 months) due to the shorter time window. However, lifetime comparison rates are directly comparable.

The rates of current and lifetime depression in the WHO were lower in the African sites (0 and 3.45 percent, respectively), which may reflect the effects of gay or bisexual orientation and drug status.

However, the rate of lifetime depression in the NCS was almost twofold higher than for the seronegatives in the WHO (17.1 and 9.4 percent, respectively).

TABLE 2. *Prevalence of major depression (current and lifetime) in the NCS and AAHP studies.*

	NCS - Total sample (male)	AAHP - Heterosexual (SN) (male)	AAHP - Gay/bisexual (SN) (Male)
Current (past 12 months)	7.7%	5.6%	16.9%
Lifetime	12.7%	11.2%	22.1%

This finding was somewhat unexpected and is still difficult to explain. It is very likely that there may be important differences in the societies and cultures studied that confer greater risk for major depression to those in the United States compared to those in other less affluent societies. It is

worth noting, however, that if the ECA rates had been used for comparison, using a similar time window, no differences would have been observed (ECA current = 2.2 percent, lifetime = 5.3 percent). Thus, some of the observed differences in the rates between the WHO and NCS samples may be due not only to differences in the time window in the societies studied, but also to possible cohort effects within the United States that are reflected in increasing rates of depression, especially among the young (Kessler et al. 1994).

The AAHP Versus the NCS

The AAHP, as noted earlier, affords an opportunity to assess a wider range of potential risk factors for major depression in men at risk for HIV/AIDS; thus it allows researchers to better estimate the relationship between HIV serostatus and major depression, while controlling for other potential cofactors. Comparisons between the findings from the AAHP and from the nationally representative sample of men in the NCS (Kessler et al. 1994) allow one to assess whether the African-American men in the AAHP evidence comparable rates of depression to those in the national referent sample.

Comparisons for current and lifetime depression for the total NCS male sample and for the gay, bisexual, and heterosexual seronegative groups in AAHP are presented in table 3. What is striking in this table is the marked similarity in prevalence rates (current, lifetime) between the NCS

TABLE 3. *Prevalence of major depression (current and lifetime) in WHO and NCS studies.*

	WHO - Zaire/Kenya heterosexual (SN)	WHO - Total sample (SN)	NCS - Total sample
Current (past 30 days)	0%	1.9%	10.3%
Lifetime	3.45%	9.4%	17.1%

and the heterosexual seronegative sample from the AAHP (current = 7.7 versus 5.6 percent, and lifetime = 12.7 versus 11.2 percent, respectively).

However, there is almost a twofold difference in the rate of major depression in the AAHP gay and bisexual groups compared to the males in the NCS for current (16.9 versus 7.7 percent, respectively) and lifetime depression (22.1 versus 12.7 percent, respectively). Interestingly, these higher rates of depression in the seronegative gays and bisexuals closely match the higher rates of depression in the female cohort of the NCS for current (16.9 versus 12.9 percent, respectively) and lifetime (22.1 versus 21.3 percent, respectively) depression.

Thus, the rates for depression among the heterosexual seronegative men in the AAHP are very similar to those obtained in the NCS, but the rates among the gays and bisexuals are strikingly higher. This provides further support for the hypothesis that being gay or bisexual appears to confer additional risk for major depression among males. A similar difference in major depression in gays and bisexuals was noted in the Atkinson and associates (1988) study, and was also suggested in the other studies in table 1 as well as in the WHO Bangkok site (Maj et al. 1994*a*). These results suggest that there may be common biological and/or psychosocial aspects of being gay or bisexual that are contributory to risk for major depression across ethnic groups. However, this conclusion is probably premature since there is suggestive evidence that being black and gay may be associated with greater risk for depression than being either black or gay. For example, results from both the ECA and the NCS indicate lower overall rates of depression in African-Americans than in white Americans (Robins et al. 1984; Blazer et al. 1994). In the NCS, the rates of major depression were significantly lower in black versus white males for current (1 month) (1.1 versus 4.0 percent) and lifetime depression (7.2 versus 13.5 percent). However, if one compares the rates for African-American males in the NCS with those for the gay and bisexual seronegatives in the AAHP, a more appropriate comparison than with the overall male sample in the NCS, one finds an even greater effect of sexual orientation than in table 3 for both current (1.1 versus 16.9 percent) and lifetime depression (7.2 versus 22.1 per-cent). Note that the Blazer and associates (1994) study used only a 30-day window for current depression in contrast to 12 months in the Kessler and colleagues (1994) study. Despite this difference in NCS case definition of current depression, the effect of sexual orientation is still provocative.

It is unfortunate that data on sexual orientation have not been reported in any of the structured diagnostic interview surveys to date, including the ECA and NCS, as well as smaller community surveys in this country (Myers et al. 1994) and in foreign countries, including Canada (Orn et al. 1988), Puerto Rico (Camino et al. 1987), Italy (Faravelli et al. 1990), New Zealand (Wells et al. 1989), and Taiwan (Hwu et al. 1986). Failure to probe for this information limits exploration of the range of key risk factors for major depression, and could artificially elevate the HIV-depression association. For example, factors such as younger age and urbanicity are both associated with being gay or bisexual and HIV-1 prevalence, and there is growing evidence linking these factors with increased risk for depression. Thus, future studies should explore the independent and combined effect of each of these variables to vulnerability to major depression.

Although much has been written on psychosocial stresses and vulnerabilities that affect the gay and bisexual populations (e.g., McKirnan and Peterson 1993), very little of this information has been incorporated into the investigation of psychiatric morbidity and HIV-1. In addition, if the psychosocial stresses and stigmatization often associated with being gay or bisexual increase one's vulnerability, then what effects are likely among African-American and other ethnic minority gays who are stigmatized both on color and on sexual orientation? The comparisons reviewed here suggest that these groups are more vulnerable to depression than heterosexuals from their own cultures. Clearly, more research is needed to pursue these initial observations.

Another question that remains unanswered in this review concerns the probable etiology of major depression in each of the studies. While the increased prevalence of lifetime depression in most of these is compatible with a pre-HIV-1, or at least a pre-AIDS, diagnosis, no study has yet reported data on family history of depression to determine whether genetic or familial factors increase the risk for mood disorders, especially in individuals whose sexual orientation may confer additional biological or psychosocial burdens. Related to this question is the unexpected finding of similar high rates of major depression (current, lifetime) between the seronegative gay and bisexual males in the AAHP and the female sample of the NCS. It is possible that some of the factors currently believed to be associated with greater female vulnerability to depression may also be applicable to gay and bisexual men. A recent study by Kendler and colleagues (1993) used multidimensional latent construct modeling techniques to predict major depression in female

twins, including biological (i.e., genetic), psychological (e.g., neuroticism), and psychosocial (history of trauma, stressful life events) predictors that may be heuristic in this regard. Some investigators have argued that some of the gender differences in vulnerability to depression may be attributed to differences in symptom reporting (i.e., women are more likely than men to report symptoms of distress that are criteria for depression), to greater dependence on social relationships and supports, to risk of trauma, and to power differences in relationships (Brown and Harris 1978; Roy 1978; Cutler and Nolen-Hoeksema 1991). Not all of these variables may be equally applicable to gays and bisexuals, but the approach could prove useful in formulating and testing explanatory and predictive models of depression in gay and bisexual males of different ethnic groups. Hopefully future studies will attempt to explain increased rates of major depression in terms of biological and/or psychosocial determinants.

There is also growing evidence of the possible priming role of abusable substances in both HIV-1 virus susceptibility (Friedman et al. 1988) and risk for major psychiatric disorders such as mood disorders (Regier et al. 1990). The results from the AAHP indicate that substance use, especially of cocaine, is a significant contributor to MDD independent of both sexual orientation and serostatus. Therefore, future studies of HIV-impacted populations should include careful assessments of patterns and severity of substance use and abuse to investigate whether the results reported here are replicated in other populations.

Finally, although the present technical review found inconsistent associations between major depression and HIV stage, the higher prevalence of major depression among gay and bisexual males, regardless of HIV stage, should be carefully investigated. It is possible that depression may confer additional risk for infection by encouraging more high-risk behaviors designed to cope with distress and dysphoria (e.g., substance use, unprotected sex with multiple partners). It may also hasten disease progression and mortality in those already infected, as suggested by studies that indicate greater resilience and longer survival in HIV-infected persons who are more hopeful and optimistic compared to the more pessimistic and dysphoric (Solomon et al. 1987; Rabkin et al. 1990). If these hypotheses are borne out, then greater attention should be given to the mental health needs of persons at highest risk for or living with HIV/AIDS, including psychiatric and substance abuse services. Hopefully, this chapter will stimulate more attention to the role of sexual orientation, substance use, and depression in HIV disease risk and progression.

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Psychiatric Symptoms, Risky Behavior, and HIV Infection

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INTRODUCTION

Previous work done at the Addiction and Research Center of the University of Pennsylvania and elsewhere has shown that the intensity and frequency of psychiatric symptoms is related to treatment outcome for patients with substance use disorders (McLellan et al. 1983; Rounsaville et al. 1986; 1987). These studies have found that patients with high symptom levels (high-severity patients) generally do poorly in standard, addiction-focused treatment. In contrast, patients with low to moderate symptom levels (low- or mid-severity patients) usually benefit considerably from addiction-focused treatments without the need for additional professional services. High-severity patients are typically characterized by significant levels of anxiety and depression and usually meet diagnostic criteria for other axis I psychiatric disorders, particularly mood disorders as described in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (APA 1994). These patients are identified as having a dual diagnosis, and most clinicians feel that their treatment outcome can be improved by adding psychiatrically focused therapy to the addiction-focused treatment that they typically receive.

Several studies have now been completed, or are in progress, to examine the benefits that may result from adding psychiatric treatments to standard drug counseling for high-severity patients. One study examined the efficacy of supportive-expressive or cognitive-behavioral psychotherapy when added to paraprofessional drug counseling in a methadone program. The results showed that high-severity patients who received only drug counseling made few gains while those who received additional psychotherapy made a number of significant gains that persisted even 6 months after therapy ended (Woody et al. 1983, 1987). A recently completed followup study gave similar results (Woody et al. 1995).

Other recent studies have examined the effect of imipramine with depressed alcoholic or opiate-addicted patients. In these, in contrast to most earlier antidepressant studies with addicts and alcoholics, the

investigators have been careful to select patients whose depression either predated their addiction or has been persistent (i.e., duration of 6 months or longer) in the context of the dependence. Preliminary results indicate that imipramine treatment has a significant effect on reducing the depression and a weaker, though measurable, effect on substance use (Nunes et al. 1991, this volume).

Taken together, this research indicates that psychiatrically impaired addicts and alcoholics (Mason and Kocsis 1991) can be helped in clinically meaningful ways by adding psychotherapy, pharmacotherapy, or combinations of both to addiction-focused treatments.

An additional line of research has examined the effect of axis II disorders, particularly antisocial personality disorder (ASPD), on outcome. Several of these suggest that patients with significant antisocial traits or a diagnosis of ASPD, like those with high levels of anxiety and depression, generally do poorly in treatment (Sturup 1948; Gibbens et al. 1959; Shamsie 1981). However, other studies also indicate that ASPD is a heterogeneous category (Gibbens et al. 1959) and that some patients with this disorder are much more responsive to treatment than others (Adams 1981). For example, Woody and colleagues (1985) found that a diagnosis of ASPD does not necessarily mean that treatment will be ineffective, although much of the available data and opinion argue that this disorder is generally associated with a less than optimal outcome.

These two types of psychiatric problems, general psychiatric severity and a diagnosis of ASPD, are often associated with poor judgment, impulsive behavior, higher levels of drug use, and other factors that increase the risk for human immunodeficiency virus (HIV) infection (Brooner et al. 1993; Metzger et al. 1993). Thus, they are a logical focus for studies attempting to identify individuals within an intravenous drug-using (IVDU) population who may be at particularly high risk for HIV infection. Put another way, these personal characteristics may provide information about why some addicts continue to share needles and engage in other behaviors that put them at risk for HIV infection, even when they know that these actions can have disastrous consequences.

Data from a study that this center has been conducting since 1989 indicate that there is a significant relationship between psychiatric symptoms and risky behavior among opioid addicts, showing that the intensity and frequency of psychiatric symptoms (i.e., psychiatric severity) is highly associated with continued needle sharing and other

risky behavior among opioid-dependent patients (Metzger et al. 1993). This finding is especially important because all of the subjects were receiving pre- and posttest HIV counseling about risky behaviors as part of an HIV testing protocol, and were well aware of the types of behaviors that put them at risk for HIV infection.

Another recent study examined HIV risk and seroconversion among heroin addicts with ASPD. This was also a prospective study involving injection drug users (IDUs) who were both in and out of methadone maintenance treatment. Results showed that addicts with ASPD engaged in significantly higher levels of needle sharing and other acquired immunodeficiency syndrome (AIDS) risk behaviors than those without this diagnosis. Moreover, subjects with ASPD became HIV positive (i.e., seroconverted) at significantly higher rates than those without the diagnosis (Brooner et al. 1993).

Overall, these studies indicate that the same factors that are associated with poor treatment outcome (i.e., high levels of psychiatric symptoms and ASPD) are also associated with higher levels of risky behavior and with actual infection by HIV.

PROCEDURES

New data on the association between psychiatric symptoms, risky behavior, and seroconversion are being obtained from the longitudinal study of heroin and cocaine addicts in Philadelphia discussed above (Metzger et al. 1993). This study is now in its fifth year and has had an 84 percent followup rate after 4 years, thus providing data continuously over an extended period of time.

The project began in 1989 at the Girard Medical Center in Philadelphia, the largest methadone program in Pennsylvania. Subject recruitment began with a random selection of 153 heroin addicts from among the 450 patients in the methadone program. After obtaining their informed consent, these 153 in-treatment (IT) subjects were asked to refer someone who "is just like you but who had been out of treatment for at least the last 10 months." Through this patient-referral method of recruitment, an additional 102 out-of-treatment (OT) subjects were identified, providing a total initial cohort of 255. All subjects were evaluated at baseline and every 6 months with a range of measures that included interviewer- and self-reported measures of HIV risk behavior, the Beck Depression Inventory (BDI)

(Beck and Beck 1972), the Hopkins Symptom Checklist-90 (SCL-90) (Derogatis et al. 1959), the Addiction Severity Index (ASI) (McLellan et al. 1980), and blood tests for HIV and human T-cell lymphocytotropic virus (HTLV) types I and II.

RESULTS

Retention

As noted, retention in this longitudinal study has been approximately 84 percent for the combined IT and OT cohorts over the first 48 months. Twenty-six subjects died during the first 4 years of the study from a range of conditions that included AIDS, homicide, drug overdose, pneumonia, and liver failure. Treatment course for many individuals has not been stable: Approximately half of the IT subjects have left treatment at some point, and approximately half of the OT subjects have entered treatment. The proportions of subjects in and out of treatment at each evaluation point are shown on figure 1.

Seroconversion

Seroconversion has been the highest (significantly so) among those who have remained out of treatment continuously and lowest among those who have continuously remained in treatment. Figure 2 shows that 30 percent of the OT subjects who began the study as seronegative and who remained out of treatment have seroconverted over the first 48 months. This compares with only 8 percent seroconversion among those IT subjects who began and remained in treatment. The two groups also showed marked differences in levels of risky behaviors such as drug use, needle sharing, visiting shooting galleries, and having unprotected sex. As seen in figure 2, seroconversions among those who moved in and out of treatment were found at rates that were not significantly different from those who continuously remained in treatment.

Psychiatric Symptoms

The intensity and frequency of psychiatric symptoms (i.e., psychiatric severity) was examined using the SCL-90, the BDI, and the psychiatric severity scale of the ASI. These measures were then studied in relation to treatment involvement, treatment entry, drug injection and needle sharing, and seroconversion. Similar relationships between each

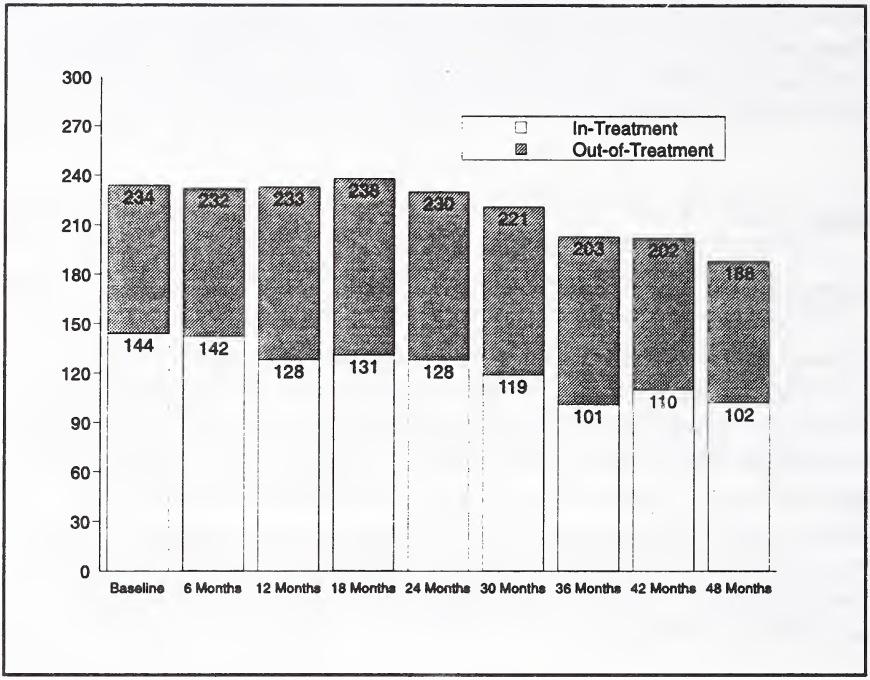

FIGURE 1. *Treatment status at time of followup.*

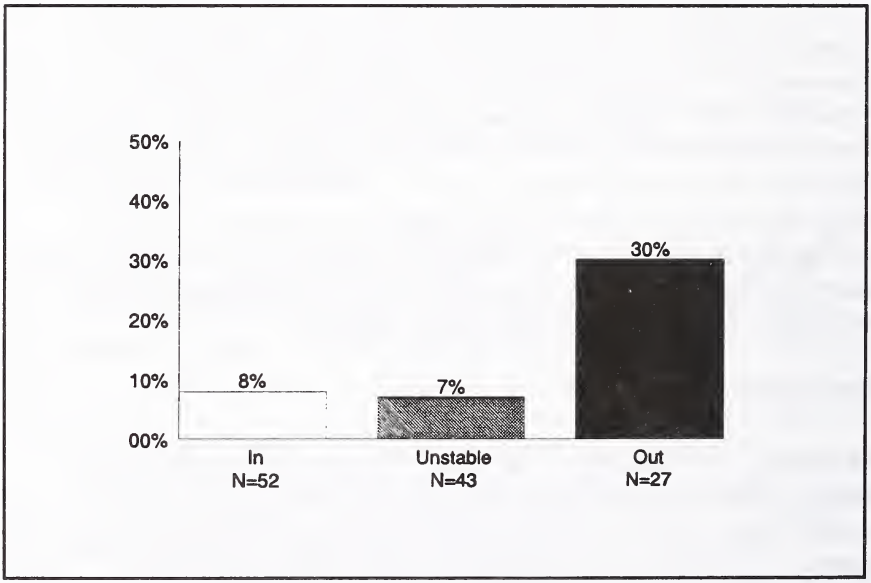

FIGURE 2. *Seroconversion by 48-month treatment patterns.*

of these domains and psychiatric symptoms were found for all measures; therefore, the SCL-90 findings will be used to demonstrate the findings.

Treatment Involvement

Patients who were in treatment had consistently higher psychiatric symptom levels than those who were out of treatment, as shown in figure 3. Psychiatric symptoms probably serve to motivate people to enter treatment because they cause discomfort that people may seek to reduce through treatment. This is consistent with other studies, in which OT substance abusers have been demonstrated to have lower levels of psychiatric symptoms than IT subjects (Rounsaville et al. 1991).

Treatment Entry

Among OT subjects, higher symptom levels were found to precede treatment entry, a finding that emerged when psychiatric symptom levels were examined at the followup point immediately preceding treatment entry among those OT subjects who subsequently entered treatment. This finding can be seen in figure 4, and it is consistent with the idea that psychiatric symptoms motivate people to enter treatment.

Injection and Needle Sharing

There was a general decline in injecting and needle sharing among both IT and OT subjects over the course of the 48 months of study, as shown in figures 5 and 6. As noted above, a subgroup continued to share needles in spite of their awareness that sharing was extremely risky behavior.

At all evaluation points, the SCL-90 scores among the injectors were higher than among those who denied injecting in the previous 6 months. These differences were significant ($p \leq 0.05$) at four of the nine evaluation points, as can be seen in figure 7. When needle sharing was examined, psychiatric symptoms were significantly higher at each of the nine evaluation points (figure 8). These findings are consistent with the idea that psychiatric severity is a significant risk factor for injecting, and especially for needle sharing—an act that is probably the single most risky behavior among these individuals.

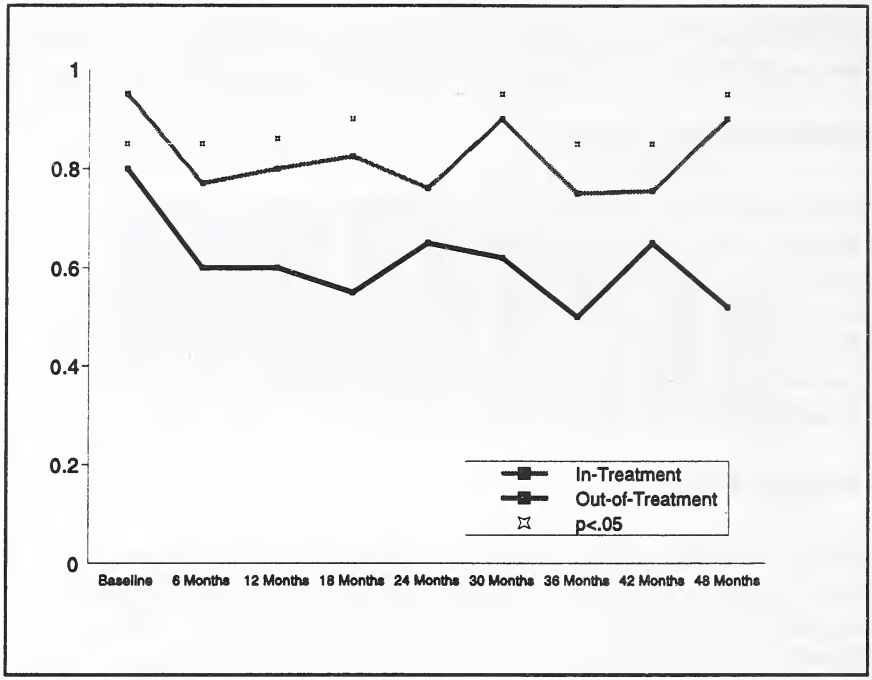

FIGURE 3. *Mean SCL-90 scores by treatment status at time of followup.*

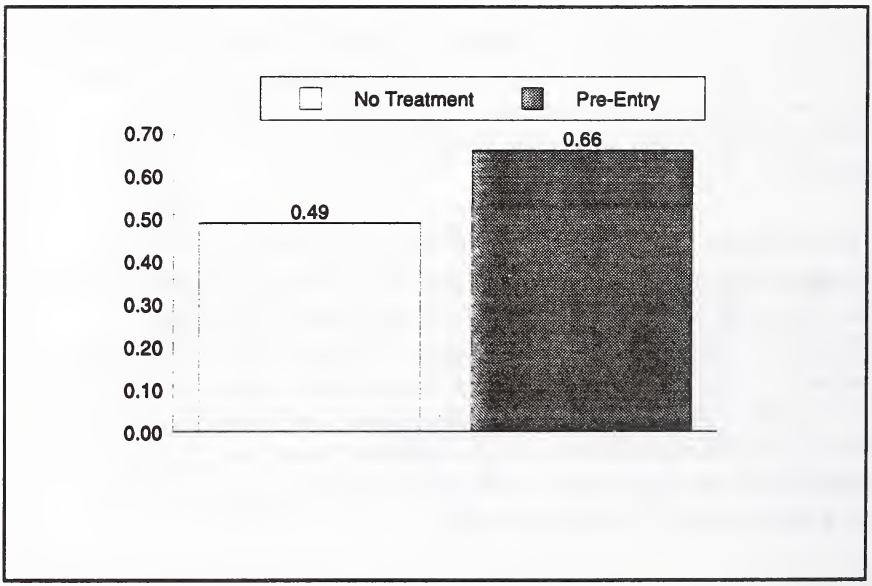

FIGURE 4. *Significantly higher ($p < 0.01$) SCL-90 scores precede treatment entry among OT subjects.*

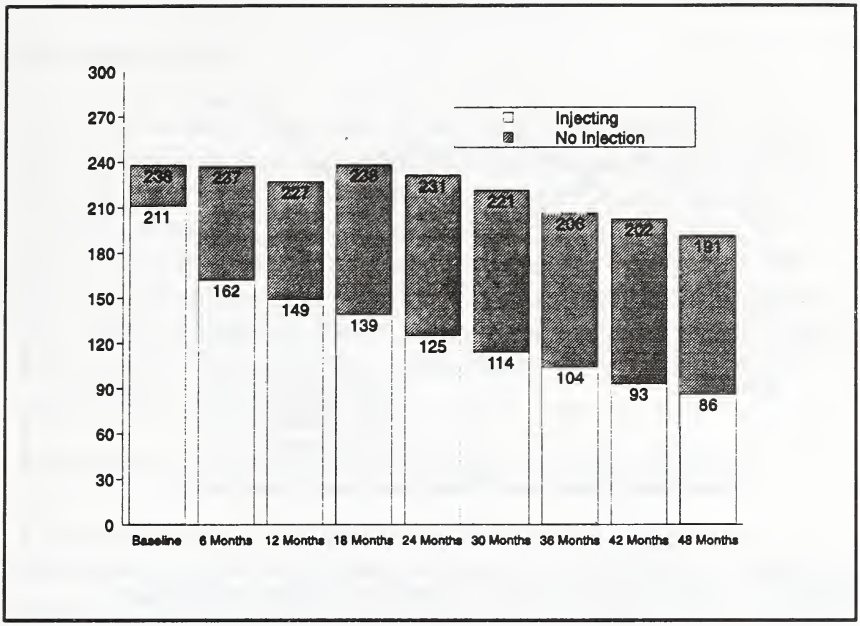

FIGURE 5. *Number of subjects injecting at followup assessment points.*

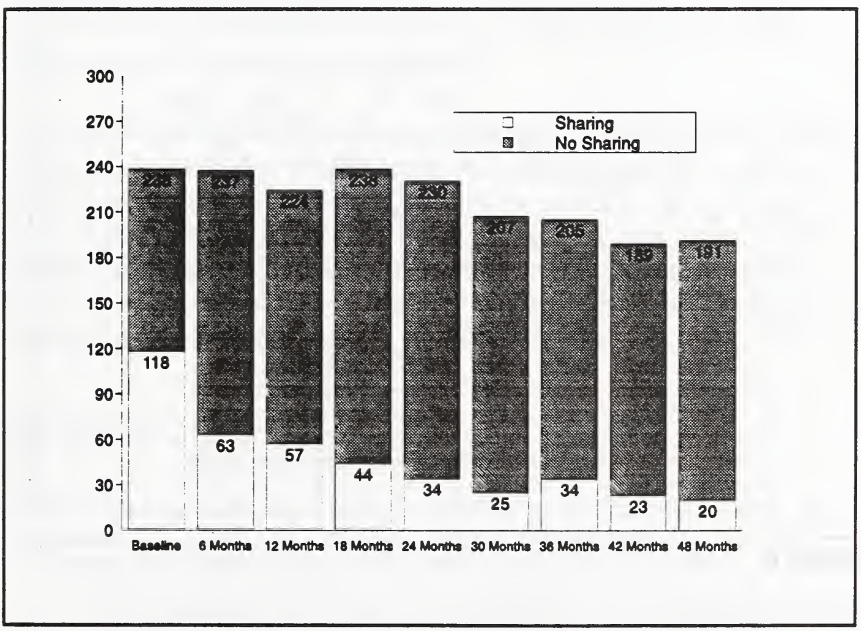

FIGURE 6. *Number of subjects sharing needles at followup assessment points.*

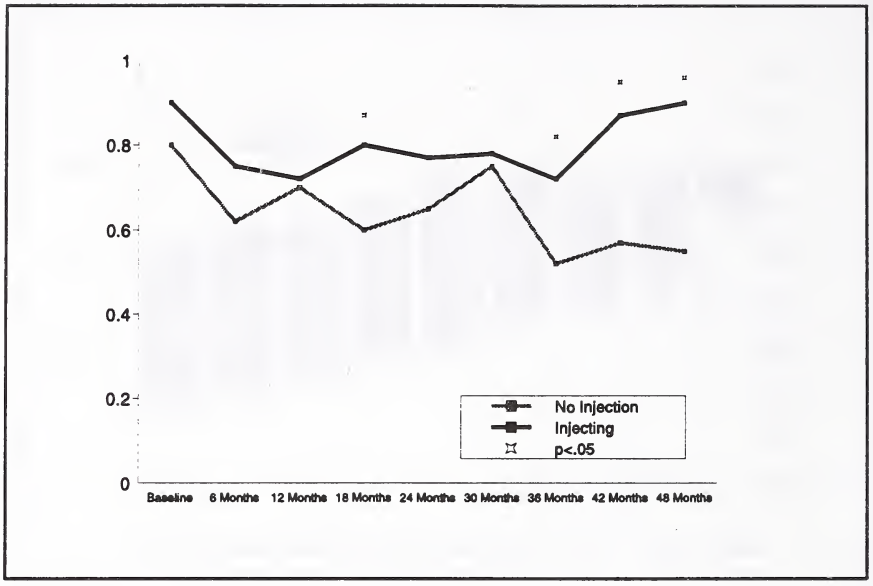

FIGURE 7. *Mean SCL-90 scores by injection at time of followup.*

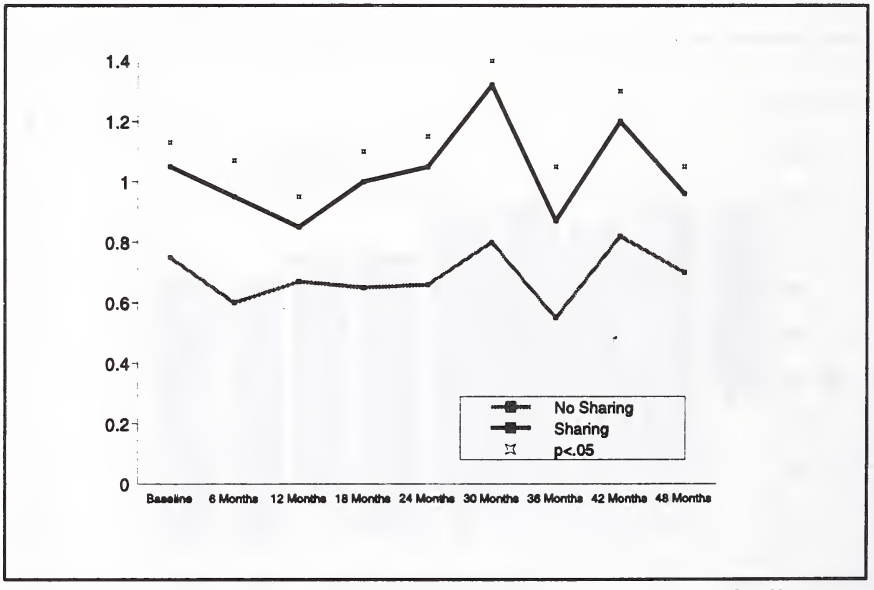

FIGURE 8. *Mean SCL-90 scores by needle sharing at time of followup.*

Seroconversion

Psychiatric severity scores were examined at the evaluation 6 months prior to seroconversion and compared with the SCL-90 scores at that same point for subjects who were of comparable sociodemographic background but who did not seroconvert. The results are shown in figure 9, and they demonstrate significantly higher average SCL-90 scores among those who seroconverted than among those who did not. This finding is consistent with those presented earlier, again suggesting that psychiatric symptoms serve as risk factors for injecting, sharing needles, and actual HIV infection.

Psychiatric Severity and Knowledge of Seropositivity

A final analysis was conducted to see whether learning that one has become seropositive is associated with increases in psychiatric symptoms. Subjects who tested positive at baseline were evaluated at each 6-month point over 24 months after being told of their serostatus. As shown in figure 10, those who became seropositive had higher SCL-90 scores at the time they tested positive than those who remained seronegative. Both negative and positive subjects showed gradual decreases in SCL-90 scores over the 24 months of followup, and there were no significant differences in scores between the groups.

Thus, in this group of predominantly male heroin addicts, learning about becoming seropositive was not associated with a persistent increase in psychiatric symptoms, in part because the symptom levels were already quite high. Clinical staff usually observed transient rises in symptoms immediately after subjects were informed of the positive test results; however, these episodes were brief and not associated with any long-term changes in psychiatric symptoms over the next 2 years.

SUMMARY

These data are internally consistent and lead to several conclusions, as follows:

- Elevated levels of psychiatric symptoms were found among IDUs in methadone treatment as compared to their counterparts who were out of treatment.

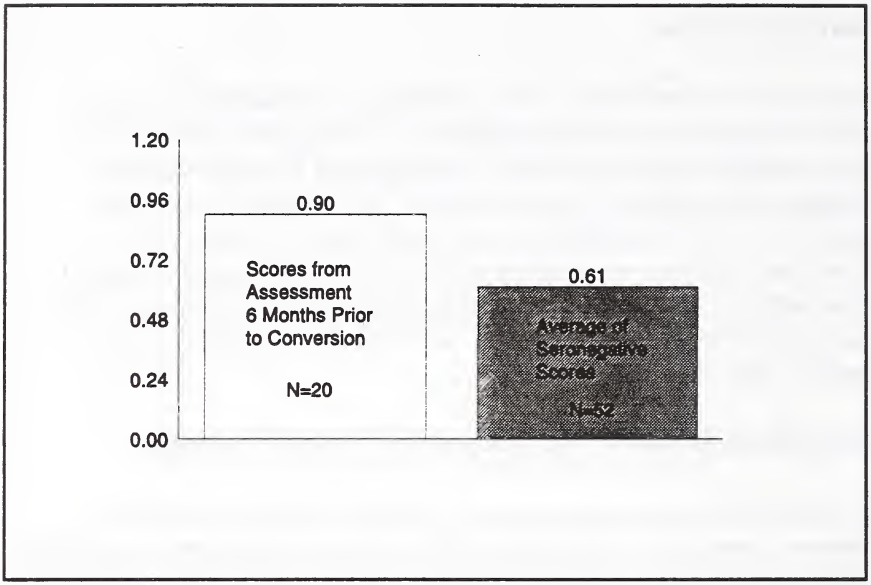

FIGURE 9. *Significantly higher ($p < 0.05$) average SCL-90 scores* precede conversion.*

KEY: * = African-American males

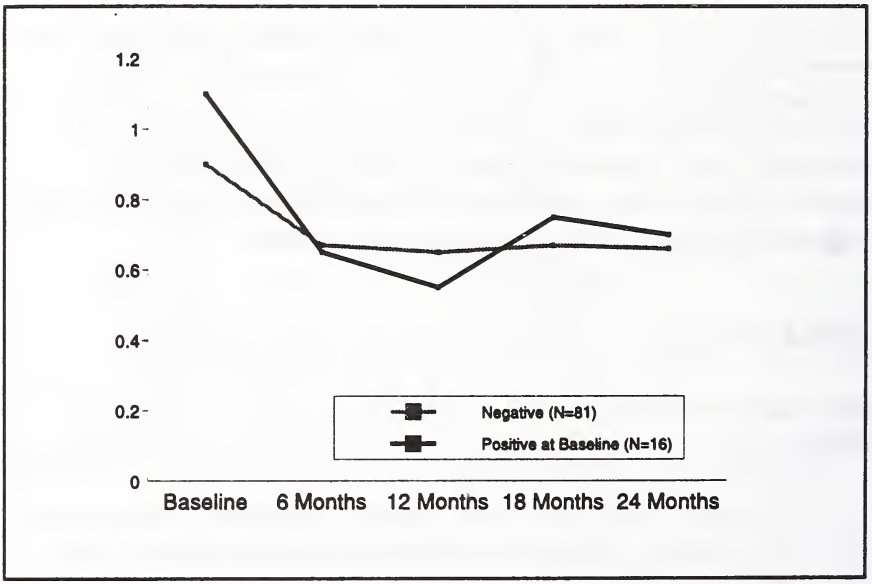

FIGURE 10. *Two-year changes in average SCL-90 scores by serostatus.*

- IVDUs who entered treatment had higher symptom levels than those who did not enter treatment.

- Higher symptom levels were found among injectors than noninjectors, and needle sharers had especially high psychiatric symptom levels.

- Higher symptom levels were found among those who seroconverted in the 6 months following notification, but not thereafter.

- Symptom levels did not distinguish between HIV-positive and HIV-negative individuals 24 months following notification of seropositivity.

Taken together, these findings indicate that elevated psychiatric symptoms are risk factors for continued high risk behavior, as well as for seroconversion. The data add to those of Brooner and colleagues (1993), who demonstrated that ASPD serves as a risk factor for HIV infection. The fact that antisocial personality disorder and psychiatric severity are associated with risky behavior and with actual HIV infection further expands earlier findings showing that these two factors are associated with poorer treatment outcome. Other axis II disorders (e.g., borderline or narcissistic), as well as other axis I disorders with high symptom levels that were not well represented in these studies (schizophrenia, manic depressive illness), may also show similar elevated rates of risky behavior and seroconversion, although there is a scarcity of data currently available to assess the risk behavior of these patients.

The evidence from treatment studies that psychiatrically focused therapies, when combined with substance abuse treatment, can improve overall outcome for patients with clinically significant levels of psychiatric symptoms may be relevant in the design of future risk reduction efforts. That is, these treatment outcome studies may serve as a starting point for exploring the feasibility and efficacy of using psychiatrically focused treatment to reduce risky behavior and HIV infection among psychiatrically symptomatic IDUs.

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